

SUPPLEMENTAL MATERIAL

Main Methods

Study participants

TOPMed

The Trans-Omics for Precision Medicine (TOPMed) program is an NHLBI-funded initiative to perform whole genome sequencing (**Supplemental Methods**) to identify genetic contributions to complex human diseases. For the current analysis, we aggregated data from about 28,000 individuals with available ECG traits including RR interval, maximum P wave duration, PR interval, QRS complex, and Bazett corrected QT interval (QTc) from standard resting 12-lead ECGs. Nine studies from the TOPMed program participated in this effort: Atherosclerosis Risk in Communities (ARIC, N=3,844), Genetics of cardiometabolic Health in the Amish (Amish, N=1,031), The Mount Sinai BioMe Biobank (BioMe, N=2,778), Cleveland Family Study (CFS, N=621), Cardiovascular Health Study (CHS, N=2,536), Framingham Heart Study (FHS, N=2,957), Jackson Heart Study (JHS, N=3,287), Multi-Ethnic Study of Atherosclerosis (MESA, N=4,473), and Women's Health Initiative (WHI, N=5,743).

UK Biobank

The UK Biobank is a large population-based prospective cohort study from the United Kingdom with deep phenotypic and genetic data on approximately 500,000 individuals aged 40-69.³⁹ Of these, 49,996 participants underwent whole exome sequencing (**Supplemental Methods**).⁴⁰ Subjects with a 3-lead exercise ECG and a 12-lead resting ECG were included in this effort. Clinical exclusion criteria and covariates in the present study were ascertained using self-report, ICD9/ICD10 codes, and operation codes (**Supplemental Methods**). The UK Biobank resource was approved by the UK Biobank Research Ethics Committee and all participants provided written informed consent to participate. Use of UK Biobank data was performed under application number 17488 and was approved by the local Massachusetts General Brigham Institutional Review Board.

We analyzed whole exome sequencing⁴⁰ and genome-wide imputed genetic data (version 3)³⁹ data from individuals with a 3-lead ECG separately from those with a 12-lead ECG. In the 3-lead cohort, ECG measurements from the resting pre-test phase of the exercise tests were extracted (**Supplemental Methods**). To maximize rigor, we included only intervals from the 3-lead ECG data which were correlated with intervals in the 12-lead ECGs (Pearson rho ≥ 0.3), among the subset that underwent both tests at different timepoints (N~4,000, **Supplemental Methods**). Although 3-lead and 12-lead ECGs were not contemporaneous (and therefore intervals are expected to differ somewhat), we excluded P wave duration and QRS duration owing to lack of correlation between 12 and 3-lead data. For these two traits, we only included individuals for whom 12-lead data were available (N=11,356). In contrast, we retained 3-lead interval data for the RR interval, PR interval, and QTc. For these traits, we retained all

individuals for whom 3-lead data were available (N=22,596); for 12-lead data we removed any individuals already included in the 3-lead cohort and any individuals determined to be 3rd degree relatives or closer to individuals with 3-lead data (KING⁴¹ kinship coefficient of ≥ 0.0442) (N=7,258 remaining). Thus, data from the 3-lead and 12-lead cohorts were from independent subjects and were combined in meta-analyses.

MyCode (DiscovEHR) study

The MyCode Community Health Initiative is an IRB-approved research study of the Geisinger health system in central and northeastern Pennsylvania. Started in 2007, the study is open to any Geisinger patient—through opt-in informed consent—including both primary and specialty care clinics, and has enrolled over 250,000 participants to date. Through the DiscovEHR collaboration with Regeneron Genetics Center, whole exome sequencing from collected blood samples has been completed for approximately 145,000 participants to date, and linked with health information from the Geisinger electronic health record, including the institutional MUSE database of 12-lead ECG data. Clinical exclusion criteria and covariates were ascertained using ICD9, ICD10 and CPT codes from the electronic health records (**Supplemental Methods**).

We removed participants with a pacemaker, Wolff-Parkinson-White Syndrome, or reported use of atrioventricular conduction affecting drugs (e.g., digoxin, class I or III antiarrhythmics). When data were available, individuals were further removed if 2nd/3rd-degree atrioventricular block or a paced rhythm was reported in the automated ECG conclusions. We finally applied additional trait-specific exclusion criteria to avoid spurious associations (**Supplemental Methods**). These exclusions were applied to TOPMed, UK Biobank, and MyCode samples.

Sample and genotype quality control

Sample and genotype quality control followed standard protocols and is summarized in the **Supplement Methods** and in **Supplemental Figures I and II**.

Single variant association analyses

Common variant analyses

We performed a genome-wide association study (GWAS) of common genetic variants (minor allele frequency [MAF $\geq 1\%$]) in the TOPMed discovery set as a means of positive control for each trait and to identify significantly associated loci within the dataset in which to prioritize subsequent gene-based tests. We used a linear mixed-effects model adjusting for the fixed effects of age, sex, history of myocardial infarction and history of heart failure, use of beta-blockers, use of calcium channel blockers, principal components 1-12. The model also implemented the random effects of empirical kinship matrix and separate residual variance components for each ancestral group using the R-package GENESIS⁴² version 2.14.3 assuming an additive genetic model. RR interval was also included in models of P wave duration, PR interval, and QRS duration. The kinship matrix was estimated using PLINK2 and the principal components were calculated by projecting related individuals to the principal components estimated from unrelated individuals using flashpca⁴³ (**Supplemental Methods**). Clinical covariates were ascertained using study-specific procedures. Individuals with missing values for the history of myocardial infarction and heart failure, beta-blockers and calcium channel

blockers were assumed to be negative for these conditions and exposures. Variants with minor allele frequencies <1% were removed from the analyses and a conventional two-sided genome-wide significance threshold ($P=5\times10^{-8}$) was used to identify significant variants.

Low frequency variant analyses

We performed single variant tests for low-frequency ($0.1\%\leq MAF<1\%$) protein-coding variants in TOPMed. We used a linear-mixed model as described above. A Bonferroni correction based on the number of variant tested was applied to determine trait-specific significance thresholds ($0.05/84,741=5.9\times10^{-7}$ for RR interval, $0.05/82,820=6.0\times10^{-7}$ for P wave duration, $0.05/83,994=5.95\times10^{-7}$ for PR interval, $0.05/84,558=5.91\times10^{-7}$ for QRS duration, $0.05/84,841=5.89\times10^{-7}$ for QTc). Variants identified in the low-frequency discovery phase were analyzed in the UK Biobank 3-lead and 12-lead cohorts using a similar linear mixed-effects model implemented in SAIGE⁴⁴ version 0.29.6. Models were adjusted for the fixed effects of age, sex, history of myocardial infarction and history of heart failure, use of beta-blockers, use of calcium-channel-blockers, and principal components 1-12 and a random effect of the empirical kinship matrix. The empirical kinship matrices were estimated using high-quality variants from the genotyping array (N=95,393 and 94,843 for 3-lead and 12-lead cohort, respectively, **Supplemental Methods**). Results from 3-lead and 12-lead data were meta-analyzed using an inverse-variance-weighted fixed-effects approach. Identified low-frequency variants were additionally analyzed in MyCode, adjusting for the same covariates. In the present analysis, we utilized MyCode to replicate low-frequency single variant associations identified in TOPMed and the UK Biobank, as well as to confirm associations and effect sizes for significantly associated low-frequency variants and genes identified using loss-of-function collapsing tests (**Figure S3**). Furthermore, findings for clinically pathogenic or likely pathogenic variants in TOPMed and the UK Biobank were also confirmed in MyCode. In a post-hoc analysis, we further carried forward a single low frequency variant in *MFGE8* for association testing with the PR interval in MyCode which could not be replicated in the UK Biobank because only a single carrier was present, after observing that the single carrier had a prolonged PR interval.

Aggregated variant association analyses

Gene-based tests at implicated loci

In our primary gene-based discovery analyses, we tested protein-coding genes residing within GWAS loci (**Supplemental Methods**) from the TOPMed single variant association analysis, and genes implicated by low-frequency variant testing. We hypothesized that rare variant associations are most likely to exist at identified common variant loci, as with previous analyses.⁴⁵ In secondary exploratory analyses, we performed exome-wide gene-based association analyses. To assess whether rare variants within genes were associated with ECG traits, we performed variant-aggregated gene-based analyses using Variant Set Mixed Model Association Tests (SMMAT),⁴⁶ implemented in GMMAT⁴⁷ version 1.1.0. In short, SMMAT performs a mixed model association test for pre-defined variant sets using an efficient hybrid between the burden test and the Sequence Kernel Association Test (SKAT), while assigning weights to variants based on MAF. Genes with a cumulative minor allele count <10 were omitted from analyses. We assumed that highly-deleterious variants would be associated with ECG traits. Variants with $MAF<1\%$ in all gene transcripts were annotated with LOFTEE⁴⁸ and

dbNSFP.⁴⁹ We analyzed variant sets consisting of both high-confidence loss-of-function (LOF) variants and missense variants that were ‘predicted-deleterious’, using a score based on 16 bioinformatics tools included in the dbNSFP dataset (**Supplemental Methods**). We included variants if 11 or more annotation tools indicated that a missense variant was deleterious. Covariates included in the analysis were identical to those used in the TOPMed single variant analysis. Bonferroni correction was applied to determine significance thresholds for the primary discovery analysis; we found 92 distinct candidate genes at associated loci in common variant association tests across all five ECG traits. Of these, 81 genes for RR interval and PR interval, 80 genes for QRS duration, and 79 genes for PWD and QTc had a cumulative minor allele count ≥ 10 . In addition, *PAM* was also tested because it was implicated in the low frequency single variant analysis. The significance threshold was therefore set to $1.23 \times 10^{-4} = 0.05 / (82 + 81 + 80 + 80)$.

We performed replication association testing for significantly associated genes in our primary TOPMed discovery analysis in the UK Biobank with adjustment for the fixed effects of age, sex, history of myocardial infarction and history of heart failure, use of beta-blockers, use of calcium-channel-blockers, and principal components 1-12 and a random effect of the empirical kinship matrix. LOF variants were restricted to those affecting canonical gene transcripts. We carried forward the *PAM* variant p.Ser539Trp (rs78408340; MAF UK Biobank=1.07%) owing to results from the low-frequency analysis suggesting that it is a functional variant. Gene based results within the 3-lead and 12-lead cohorts were meta-analyzed using the ‘SMMAT.meta’ function in the R-package GMMAT. We additionally performed a leave-one-variant-out analysis to assess the influence of individual variants on gene-based associations (**Supplemental Methods**).

Loss-of-function gene-based collapsing tests

For genes associated with an ECG trait in both TOPMed and UK Biobank, we then assessed whether LOF variants in the gene were associated with the respective trait by classifying individuals as carriers or non-carriers to estimate the effect of deleterious variation in these genes (**Supplemental Figure III**). We performed tests in which rare (MAF<0.1%) LOF variants in canonical gene transcripts were collapsed into a single variable (carrier versus noncarrier) for each individual in TOPMed and UK Biobank. Collapsed tests were performed with linear mixed-effects models in the same manner as for the single variant analysis. Results were meta-analyzed across TOPMed and UK Biobank using an inverse-variance weighted fixed-effects approach. Significant results were subsequently replicated in MyCode, and an inverse-variance weighted fixed-effects meta-analysis was subsequently performed across all studies. Since no LOF variants were identified for *KCNE1* in TOPMed or UK Biobank, we performed a collapsing test for predicted-deleterious missense variants for this gene alone.

Putative long QT syndrome genes and other clinically relevant variation

We also performed gene-based tests for 17 genes from a typical commercially available long QT syndrome gene panel using the aggregated gene based tests described above.¹⁶ These genes included *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *KCNJ5*, *CACNA1C*, *CAV3*, *TRDN*, *CALM1*, *CALM2*, *CALM3*, *SNT1A*, *ANK2*, *AKAP9*, *SCN4B*. We assessed whether low-

frequency and rare (MAF<1%) predicted-deleterious coding variants in these genes were associated with the QTc using SMMAT in TOPMed, with replication in UK Biobank.

We further curated pathogenic and likely pathogenic variants in long QT syndrome panel genes¹⁶ from ClinVar (Downloaded July 2019). Variants were limited to those submitted from clinical testing labs and evaluated as of 2015 or later. We quantified the effect of pathogenic and likely pathogenic variants using collapsed tests in TOPMed, UK Biobank, and MyCode. In addition, we combined carrier status of three genes in which incidental variant discovery is reportable per the American College of Medical Genetics and Association of Molecular Pathologists (*KCNQ1*, *KCNH2*, and *SCN5A*) for long QT syndrome.²⁵ We performed linear mixed-effects models in TOPMed, UK Biobank, and MyCode, and meta-analyzed the results using an inverse-variance weighted fixed-effects approach. We further performed analyses where carrier status for LOFs and pathogenic and likely pathogenic variants were pooled for carrier status of *KCNQ1* and *KCNH2*, each of which were associated with QTc (see below).

We also calculated the proportion of LOF, pathogenic, and likely pathogenic variant carriers with QTc prolongation in each gene. We examined both 1) prolonged QTc (QTc \geq 460ms, 480ms, 500ms) and 2) the 99th percentile of sex-specific QTc (male: QTc \geq 468ms, female: QTc \geq 482ms, from the UK Biobank). We defined penetrance as the proportion of mutation carriers with a prolonged QTc. We also calculated the proportion of rare variant carriers among individuals with prolonged QTc (again, for \geq 460ms, 480ms and 500ms). For this analysis we first focused on carriers of LOF, pathogenic or likely pathogenic variants in *KCNQ1* and *KCNH2*. Because this analysis only considers known, adjudicated variation in *KCNQ1* and *KCNH2*, we then repeated the analysis while i) including any rare (MAF<0.1%) protein-altering genetic variant in these genes, as well as ii) any rare protein-altering variant in any of the LQTS panel genes. Protein-altering variants included any missense, inframe indel, frameshift indel, stopgain, stoploss, startloss or splice variant.

We further estimated the relative odds of QTc prolongation among mutation carriers as compared to noncarriers using Firth's logistic regression⁵⁰ in TOPMed, UK Biobank, and MyCode. For Firth's logistic regression analyses, we only used individuals who were genetically determined to be unrelated from one another. For the TOPMed and UK Biobank cohorts, relatedness was determined using a KING⁴¹ coefficient cutoff of 0.0442, while in MyCode relatedness was determined using an identity-by-descent PI_HAT cutoff of 0.1875. We present meta-analyzed data from TOPMed and the UK Biobank separately from MyCode for this analysis. We plotted the distribution of QTc among carriers and noncarriers in a pooled set of TOPMed and UK Biobank participants; we replicated the same analyses in MyCode. Similar analyses were conducted for the PR interval and clinically pathogenic, likely pathogenic and LOF variants in the *SCN5A* gene, which was associated with PR duration (from **Results**).

Extended Methods and Results

Supplemental Methods

Sample level quality control (QC) for TOPMed

Sequencing and variant calling procedures for TOPMed is provided in the official TOPMed website: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970000/>.

TOPMed previously performed whole-genome sequencing of 107,047 samples in freeze 6. Of those samples, the information research center in Michigan kept 101,326 samples passing initial quality control. We found 9 cohorts with 30,025 samples who were willing to participate in the current study. Of those samples, 514 did not have information for the 5 ECG traits. From this dataset, samples with variant missingness rate <5% and allele counts >0 were subjected to additional sample and variant level quality control. Duplicated pairs of samples were estimated with KING2⁴¹ using a pruned variant set (see below in *Estimation of genetic ancestry for TOPMed*). We removed one sample from a duplicated pair when the pair was not a monozygotic twin. Genetically determined sex was estimated using independent variants with MAF ≥5% and missingness ≤1% on chromosome X. Participants with a mismatch between reported and genetically determined sex were removed from the dataset. We further calculated quality control matrices such as the heterozygosity homozygosity ratio, transition and transversion ratio, SNP and Indel ratio, and the number of singletons per sample. Samples beyond 8 times the standard deviation from the mean of the quality control matrices were excluded from the dataset. In the present QC, 39 individuals were duplicated, 5 samples had missing genotype rate >5% and 21 samples had a sex mismatch. After calculating the heterozygosity / homozygosity ratio, transition / transversion ratio, SNP / Indel ratio, and the number of singletons for QC matrices, 4 participants who were 8 standard deviations or more apart from the mean of the matrices were removed. In total, 29,442 samples remained after sample level QC.

Estimation of genetic ancestry for TOPMed

To determine genetic ancestry, we used a pruned variant set. We selected variants with MAF ≥5% and missingness rate <1% that were presented in both TOPMed and the 1000G dataset.

We sequentially pruned variants for European, East Asian, South Asian, Admixed American,

and African American in 1000G dataset using “--indep-pairwise 50 5 0.2” option in PLINK.⁵¹

ADMIXTURE⁵² learned the genetic structure of the 5 ethnic groups using the pruned variants in 1000G dataset and projected the TOPMed participants on the 5 reference ethnic groups. We classified individuals into 5 reference populations when the probability of an ethnic group was greater than 80%. Individuals with the probabilities <80% for all ethnic groups were classified as “Undetermined”. We did not include Amish in this estimation because this cohort is known to be a homogeneous cohort. In sum, we classified all TOPMed participants into Amish, European, East Asian, South Asian, Admixed American, African American, and Undetermined groups.

Variant level quality control for TOPMed

We removed any variant located in a low complexity region and performed Hardy-Weinberg equilibrium tests by ethnic group. Variants with Hardy-Weinberg testing $P < 1 \times 10^{-6}$ within ancestral groups were removed from the dataset. We did not perform the Hardy-Weinberg test in the South Asian ancestry group due to small sample size ($N=63$). In the present QC, 439,583 variants located in low complexity regions were removed, 8,040 variants were removed because they failed the Hardy-Weinberg Equilibrium test, as well as 2 million variants that were monomorphic in the final dataset, leaving 294 million variants.

Estimation of principal components for TOPMed

With a set of pruned variants, we identified unrelated individuals using a KING⁴¹ kinship coefficient cutoff of 0.0442. We calculated the variant loadings, their mean and standard deviation, and estimated the principal components of the unrelated samples using flashPCA.⁴³ Subsequently, principal components were projected onto related individuals.

Sample and variant QC in UK Biobank

We restricted our analyses in the UK Biobank to individuals of European ancestry, as determined by previous principal component analysis.⁵³ We additionally excluded individuals who did not have high-quality genotyping array data. For example, we excluded those with a mismatch between genetically determined and reported sex, outliers for missingness or heterozygosity, individuals with putative sex-chromosome aneuploidy, and those not included in the UK Biobank's centrally provided estimation of relatedness. For analysis of whole exome sequencing data, the 'functionally-equivalent' dataset was used. This dataset was previously created according to the primary analysis protocol⁵⁴ and was subject to GATK 3.0 variant calling (variants were annotated to genome build GRCh38). Variants with inbreeding coefficient <-0.03 or without at least one variant genotype of read depth ≥ 10 , genotype quality ≥ 20 and, if heterozygous, allelic balance ≥ 0.20 were filtered out

(<https://biobank.ctsu.ox.ac.uk/showcase/label.cgi?id=170>). It has been reported that the initial version of this dataset is missing a number of variants, specifically in regions of the genome with multiple alternate haplotypes, but we proceeded with this version as most genes are unaffected and a new FE file had not yet been released at the time of this writing. We further removed variants with call rates $< 90\%$ and those failing the Hardy Weinberg Equilibrium test ($P < 1.0 \cdot 10^{-15}$).

Quality control for the kinship matrix in the UK Biobank

A subset of high-quality variants from the genotyping array was used to estimate the genetic relatedness matrix for UK Biobank participants. Variants with MAF $< 1\%$, missingness $> 1\%$ or that failed a stringent HWE test ($P < 0.001$) were removed. Variants present in the MHC or the chromosome 8 inversion regions of the genome were additionally excluded. Finally, two rounds of linkage-disequilibrium-based pruning were performed (`--indep-pairwise 200 100 0.1` and `--indep-pairwise 200 100 0.05` in PLINK2.0⁵¹). After quality control, 95,393 and 94,843 high-quality independent variants remained for the 3-lead ECG cohort ($N=22,596$) and the 12-lead ECG cohort ($N=7,258$), respectively. For all analyses in GENESIS²⁴ and GMMAT,²⁵ kinship matrices were estimated with these variants using PLINK2.0.

Sample and variant QC in MyCode

We restricted our analyses to individuals with whole exome sequencing⁵⁵ and resting 12-lead ECG data. Sample-level variant quality filters were applied to enforce a minimum alternate allele balance of 20% and minimum alternate read depth of 5. When multiple ECGs were available for a given participant, data from the most recent study were used. General and trait-specific exclusions were applied.

Clinical covariates and exclusion criteria

Clinical covariates and exclusion criteria in TOPMed cohorts were defined using study-specific feature definitions. Data were centrally collected and harmonized prior to analysis.

In the UK Biobank, myocardial infarction was defined using the central algorithmically-defined outcome for myocardial infarction (field 42001;

<https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=42001>) including self-reports, hospital admissions and death records. Heart failure was defined using: self-reported non-cancer illness codes 1076, 1079 and 1588; ICD10 codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, I50, I50.0, I50.1 and I50.9 among main diagnoses, secondary diagnoses, primary causes of death and secondary causes of death; and ICD9 codes 4254, 4280, 4281 and 4289 among main and secondary diagnoses. Presence of cardiac pacemaker was defined using: self-reported presence of pacemaker during interview; self-reported operation codes 1096, 1548 and 1549; ICD10 code Z45.0 among main and secondary diagnoses; operative procedure codes K60, K60.1, K60.2, K60.3, K60.4, K60.5, K60.6, K60.7, K60.8, K60.9, K61, K61.1, K61.2, K61.3, K61.4, K61.5, K61.6, K61.7, K61.8 and K61.9 among main and secondary OPCS. Wolff-Parkinson-White syndrome was defined using: self-reported non-cancer illness code 1484; ICD10 code I45.6 among main diagnoses, secondary diagnoses, primary causes of death and secondary causes of death; ICD9 code 4267 among primary and secondary diagnoses; operative procedure codes K52.4 and K57.4 among main and secondary OPCS.

In MyCode, myocardial infarction was defined using the following codes (2 or more had to be present): ICD9 codes 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22,

410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 412, 429.79; ICD10 codes I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I24.1 and I25.2.

Heart failure was defined using the following codes (2 or more had to be present): ICD9 codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.33, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41,

428.42, 428.43, 428.9; ICD10 codes I09.81, I11.0, I13.0, I13.2, I50, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43 and I50.9. Wolff-Parkinson-White syndrome was defined using the following codes (2 or more had to be present): ICD9 code 426.7 and ICD10 code I45.6. Pacemaker presence was defined using the following codes (either 2 or more ICD9/10 codes or 1 CPT code): CPT codes 33200, 33206, 33207, 33208,

33212, 33214, 33217, 33222, 33227, 33228, 33229, 33233, 33234, 33235, 33236, 33237, 71090, 93279, 93280, 93281, 93286, 93288, 93293, 93294, 93610, 93731, 93732, 93733,

93734, 93735, 93736; ICD10 codes Z45.01, Z45.010, Z45.018, Z45.0; ICD9 codes 37.8, 37.85, 37.86, 37.87, 37.89, 996.01, 37.87 and 37.89.

Trait-specific ECG exclusions

Apart from general exclusions, we also applied trait-specific exclusion criteria (**Supplemental Figure I**). For RR interval, we excluded individuals with RR<600 and RR>1500. For PWD, we excluded individuals with PWD<40 or PWD>180. For PR interval, we excluded individuals with PR<80 or PR>320. For QRS, we removed individuals with QRS<60 or QRS>150. For QTc interval, we removed individuals with QRS>120, heart rate<40 or heart rate>120.

Extracting ECG parameters from 3-lead exercise ECG in the UK Biobank

We extracted ECG intervals that were automatically generated by GE exercise ECG machine. To identify baseline measurement (pretest stage), which is equivalent to resting ECG measurement, we found stages with Load=0, Grade=0 when it was not in a recovery stage. If there were multiple measurements at this stage, we took the earliest observation.

Correlation between 3-lead and 12-lead ECG data in the UK Biobank

To assess the quality of 3-lead ECG data in the UK Biobank, we calculated Pearson's correlations between 12-lead and 3-lead data for each trait among individuals who underwent both tests. For RR interval (N=4,036) 12-lead and 3-lead data showed a correlation of 0.58 ($P<2.2\times10^{-16}$), while the PR and QTc intervals showed correlations of 0.64 (N=3,955, $P<2.2\times10^{-16}$) and 0.39 (N=4,036, $P<2.2\times10^{-16}$), respectively. As these correlations were greater than 0.3, we kept both 3-lead and 12-lead data for these three traits. For PWD and QRS, correlations were 0.06 (N=3,956, $P=1.2\times10^{-4}$) and 0.17 (N=4,045, $P<2.2\times10^{-16}$), respectively. For these traits we deemed the 3-lead data of low quality, and only 12-lead data was used for any analysis in the UK Biobank.

Defining candidate loci for gene-based analysis

For each ECG trait, we performed genome-wide association tests in the TOPMed dataset for variants with MAF>0.1% and found variants reaching the conventional genome-wide significance level ($P<5\times10^{-8}$). First, we identified the most significant variants among the genome-wide significant variants. Within +/-1Mbp from this leading variant, we selected two variants 1) at the beginning of the genome-wide significance signal and 2) at the end of genome-wide significance signal. For the first variant, we calculated the r^2 for variants located at 60kb upstream and chose the first variant with $r^2\geq0.3$. For the last variants, we estimated the r^2 for variants located at 60kb downstream and selected the last variant with $r^2\geq0.3$. Anything between these first and last variants was defined as a locus. We subsequently performed the same algorithm until all of the variants that reached the genome-wide significance level were assigned to their locus. We determined the loci for each trait and identified genes that were located at these loci. We combined genes that were found for 5 ECG traits and defined these genes as candidate ECG loci for gene-based analysis.

Calculating predicted-deleterious score for missense variants using tools in dbNSFP

For gene-based tests, missense variants were considered deleterious if they attained at least a score of 11 out of 16 based on 16 bioinformatics prediction tools in the dbNSFP dataset.⁴⁹ If one tool predicted a variant to be damaging, a point was added to the score. If no tools predicted a given variant to be damaging, the variant would have a score of 0; if all tools predicted a given variant to be damaging it would have a score of 16. The following tools and criteria were used: VEST3>90%; CADD>90%; DANN>90% Eigen-raw>90%; Eigen-PC-raw>90%; FATHMM pred=D; FATHMM-MKL pred=D; PROVEAN pred=D; MetaSVM pred=D; MetaLR pred=D; MCAP>0.025; PolyPhen HDIV pred=D; PolyPhen HVAR pred=D; SIFT pred=del; LRT pred=D; MutTaster pred=D or A.

Leave-one-variant-out analysis

We performed a leave-one-variant-out analysis for genes significantly associated with an ECG interval by iteratively removing a variant from the aggregated variant group and repeating SMMAT as outlined above. We visually inspected the strength of association between the gene across each remaining variant set, to assess the relative contribution of each variant to the original association. We considered attenuation of the association between the gene and the ECG interval if the association decreased by at least 0.5 on the -log₁₀ (*P*-value) scale, or if the gene-based test no longer reached nominal significance (≥ 0.05).

Supplemental Results

Replication results for a common variant locus of QRS duration

In the primary analysis of common variants, we identified a novel association with QRS duration at conventional genome-wide significance: rs117398559 near *MAFB* (prolonging allele=A, $\beta=2.28$ ms, $P=3.1\times 10^{-8}$, MAF=1.6%). In the UK Biobank 12-lead ECG data, rs117398559 was not present although another SNP, rs62210619, was present which is in high linkage disequilibrium ($R^2>0.8$) with rs117398559. rs62210619 did not show evidence of association with QRS duration in UK Biobank ($\beta=0.05$ ms, $P=0.93$, MAF=2.5%).

Association results for low-frequency variants

We sought to determine whether any low-frequency ($0.1\% \leq \text{MAF} < 1\%$) variants in protein-coding regions were associated with studied ECG traits (**Supplemental Figure XI**). We identified an association between a missense variant in *PAM* (p.Ser539Trp; rs78408340) and the PR interval ($\beta=7.96$ ms, $P=1.90\times 10^{-7}$, MAF=0.47%; **Supplemental Table V**). rs78408340 had higher MAF in individuals of European (0.66%) than African (0.09%) ancestry, but we observed comparable penetrance of first-degree atrioventricular block (PR interval ≥ 200) in individuals of European (35/220=16%) and African (2/10=20%) ancestry. In the UK Biobank ($\beta=2.33$ ms, $P=0.012$) and MyCode ($\beta=3.3$ ms, $P=1.80\times 10^{-4}$) this association was present with the same direction of effect. *PAM* is highly expressed in the heart and the locus has previously been associated with the PR-interval in common variant GWAS.¹² rs78408340 has previously been associated with Type 2 Diabetes through lowered *PAM* expression.⁵⁶ A rare synonymous variant in *MFGE8* (rs141997845) was associated with marked prolongation of the PR interval in the TOPMed dataset ($\beta=19$ ms, $P=4.9\times 10^{-8}$, MAF=0.1%; **Supplemental Table V**). The MAF of rs141997845 was lower in individuals of European (0.039%) than African (0.277%) ancestry while the penetrance of first-degree atrioventricular block was higher in individuals of European (7/13=53.8%) than African (7/28=25%) ancestry. Although only a single carrier was identified in the UK Biobank, this carrier had a PR interval consistent with first-degree atrioventricular block (PR interval=200 ms; 2.35 SD from the mean in the 3-lead cohort). In MyCode, this association was present with the same direction of effect ($\beta=15$ ms, $P=1.6\times 10^{-3}$). Common variants near *MFGE8* have been identified in a coronary artery disease GWAS.⁵⁷ Furthermore, *Smad3* knock-out mice have modestly prolonged PR-intervals and their macrophages exhibit lower expression of *Mfge8*.⁵⁸ We observed that common variants in *PAM* and *MFGE8* were associated with PR interval at nominal significance (**Supplemental Figure XII**).

Gene-based test replication in UK Biobank

In the UK Biobank whole exome sequencing data using gene-based SMMAT, we did not perform an association test between *HAND1* and P-wave because of low cumulative allele count (cMAC=4). *CR1L* did not associate with QRS duration ($P = 0.91$, **Supplemental Table VI**). Because we did not find evidence for these genes in both TOPMed and UK Biobank using SMMAT, we did not put these genes forward for LOF collapsing analyses. While *HAND1* is a strong candidate because of its role in the structural and electrophysiological development of the heart,⁵⁹ larger sample sizes may be needed to replicate this finding.

Gene-based test for genes previously reported for long-QT syndrome (LQTS)

While a range of genes have previously been implicated in monogenic forms of LQTS, the role for some of these is contested.¹⁰ We performed gene-based SMMAT to see whether predicted-deleterious variants with MAF<1% in LQTS panel genes was associated with the QT interval. Besides *KCNQ1* and *KCNH2*, only predicted-deleterious variation in *KCNE1* showed robust evidence of association with the QT interval (TOPMed: N variants=9, cMAC=29, $P=1.24\times 10^{-4}$; UK Biobank: N variants=8, cMAC=24, $P=9.03\times 10^{-5}$; **Supplemental Table X**). After performing leave-one-variant-out analysis for *KCNE1* (**Supplemental Figure XIII**), we found two missense variants (rs74315445; p.Asp76Asn and rs1199519166; p.Lys69Glu) contributing to the association with the QTc interval in TOPMed. We found 6 carriers of p.Asp76Asn, which on average had a 460ms (SD=27) QTc interval. One had a corrected QTc interval consistent with LQTS (≥ 480 ms). p.Asp76Asn has been submitted to the ClinVar database, with 6/7 interpretations being pathogenic (4) / likely pathogenic (3). For p.Lys69Glu, we found one carrier who had a QTc interval of 486ms. Neither of these variants was present in the UK Biobank.

Along with *KCNQ1* and *KCNH2*, *SCN5A* is considered one of the classical LQTS genes. Interestingly, predicted-deleterious variants in *SCN5A* were not associated with the QTc interval in either dataset (TOPMed: N variants=193, cMAC=1055, $P=0.13$; UK Biobank: N variants=110; cMAC=417; $P=0.67$). One interpretation is that that bioinformatics predictions of deleteriousness are not adequate for genes in which loss-of-function alleles are not expected to affect a given trait; this is the case for *SCN5A*, a gene in which mainly gain-of-function alleles have been reported to markedly affect QTc duration.¹¹ Another interpretation is that larger sample sizes will be required to uncover additional associations between the ECG and rare variants. The need for larger sample sizes is especially true for genes in which very few carriers of deleterious variants were identified, such as *CALM1* and *CALM2*.

LOF collapsing tests for SCN5A and PAM for PR interval

Abnormalities in atrioventricular conduction are associated with an increased risk of atrial arrhythmia.³ Following the identified association between PR interval and *PAM* and *SCN5A* in TOPMed and UK Biobank using SMMAT, we aimed to quantify the effect of rare (MAF<0.1%) LOF variants on atrioventricular conduction, using collapsed tests. LOF variants in the canonical transcript of *PAM* were significantly associated with the PR interval in TOPMed and UK Biobank ($\beta=-13$ ms; $P=4\times 10^{-3}$; N carriers=29; **Supplemental Table VII**). This finding did not replicate in MyCode, as *PAM* LOF variants showed an insignificant prolonging of the PR interval in this dataset ($\beta=8$ ms; $P=0.2$, N carriers=23; **Supplemental Tables VII-VIII**). Rare LOF variants in the canonical transcript of *SCN5A* conferred a 22 ms prolongation of the PR interval across TOPMed and UK Biobank dataset ($P=2.7\times 10^{-6}$, N carriers=27; **Supplemental Tables VII**). Although associated with a strong prolongation of the PR interval, only 3/9 carriers in the TOPMed dataset and 4/18 carriers in the UK Biobank had first-degree atrioventricular block, as defined by PR interval ≥ 200 ms. In MyCode, *SCN5A* LOFs were significantly associated with prolongation of the PR interval as well, albeit with larger effect (N carriers=43, $\beta=51$ ms, $P=2.9\times 10^{-33}$, **Supplemental Tables VII-VIII**).

LOF collapsing tests for KCNQ1, KCNH2 and KCNE1 for QTc interval

We identified associations between QTc interval and *KCNQ1*, *KCNH2* and *KCNE1* in TOPMed and UK Biobank using SMMAT. We then aimed to quantify the effect of rare (MAF<0.1%) LOF variants on ventricular repolarization, using collapsed tests (**Supplemental Table VII**). *KCNQ1* LOF variants in the canonical transcript markedly prolonged the QTc interval across TOPMed and UK Biobank (N carriers=27, $\beta=41$ ms, $P=8.2\times 10^{-21}$, **Supplemental Tables VII-VIII**). 4/16 carriers of *KCNQ1* LOF variants in TOPMed and 3/11 carriers in UK Biobank had corrected QT intervals ≥ 480 ms, to suggest LQTS. *KCNH2* LOF variants in the canonical transcript were associated with marked QTc prolongation across TOPMed and UK Biobank as well (N carriers=11, $\beta=32$ ms, $P=4.0\times 10^{-6}$, **Supplemental Tables VII-VIII**); 2/5 carriers in TOPMed and 0/6 carriers in UK Biobank had QTc intervals ≥ 480 ms. In MyCode, results for both these genes replicated, as LOFs in *KCNQ1* and *KCNH2* were significantly associated with QTc prolongation ($\beta=43.40$ ms, $P=1.7\times 10^{-24}$ and $\beta=50.70$ ms, $P=1.2\times 10^{-7}$, respectively; **Supplemental Table VII-VIII**). No LOF variant carriers were identified for *KCNE1* in TOPMed or UK Biobank, so this gene was not put forward for LOF collapsing tests in MyCode.

Pleiotropy of SCN5A and MYH6 variants in gene-based testing in TOPMed

Gene-based SMMAT also highlighted pleiotropic conduction associations for clinically important genes. Along the significant association between *SCN5A* and PR interval, this gene was further associated nominally with QRS duration ($P=0.026$; previously reported¹⁴) and P-wave duration ($P=5.7\times 10^{-4}$; not previously reported) in TOPMed (**Supplemental Table VI**). Similarly, the cardiac sarcomeric gene *MYH6* was nominally associated with three traits in TOPMed, namely RR interval ($P=0.001$; previously reported⁶⁰), PR interval ($P=0.006$; previously reported⁶¹) and P-wave duration ($P=0.04$; not previously reported) (**Supplemental Table VI**). Rare *MYH6* variants have previously been implicated in the development of cardiomyopathy⁶² as well as congenital heart disease.⁶³ Because of the observed pleiotropy of *SCN5A* in both common variant analysis and gene-based SMMAT, we used collapsed tests to assess the effect of rare *SCN5A* LOF variants on the remaining four traits (P-wave duration, QRS duration, QTc interval, RR interval). We found that *SCN5A* LOF variants further were associated with markedly prolonged P-wave duration ($\beta=16$ ms, $P=4.4 \times 10^{-14}$) and QRS duration ($\beta=14$ ms, $P=4.7 \times 10^{-16}$) across TOPMed, UK Biobank and MyCode using inverse-variance weighted fixed-effects meta-analysis (**Supplemental Table XVI and Figure VII**).

Exome-wide gene-based tests in TOPMed and replication in UK Biobank

In secondary analyses, we performed gene-based tests for all genes with cumulative minor allele counts ≥ 10 in the genome. Other than *PAM* and *SCN5A* for PR interval and *KCNQ1* and *KCNH2* for QTc interval, 28 genes were associated with ECG traits in TOPMed at exome-wide significance (1 for P-wave duration, 4 for PR interval, 6 for QRS duration, 17 for QTc interval, **Supplemental Table IX**). Of 28 significant genes in TOPMed, 3 genes that did not have a high enough cumulative minor allele count, and were excluded from the replication analyses in UK Biobank. Among the remaining 25 genes (1 for P-wave duration, 3 for PR interval, 6 for QRS duration, 15 for QTc interval) tested for associations in UK Biobank, none reached nominal significance ($P<0.05$) and therefore no new genes were put forward for LOF collapsing tests.

Estimating the magnitude of effect of KCNE1 predicted-deleterious missense variants

Because no LOF variant carriers were identified for *KCNE1* in TOPMed or UK Biobank, we aimed to estimate the effect size of the predicted-deleterious missense variants that were included in the gene-based test, under the assumption that they confer the same direction of effect. We performed a collapsed test for these missense variants and meta-analyzed results from TOPMed and UK Biobank using an inverse-variance weighted approach. Across these studies, predicted-deleterious missense variants were associated with a 16 ms prolongation of the QTc interval ($P=3.32\times 10^{-7}$; N carriers=52) (**Supplemental Table XI**). Among 28 carriers in TOPMed, 3 had QTc \geq 480 ms (11%), while in the UK Biobank 1/25 (4%) of carriers had such a QTc interval (**Supplemental Tables XII**). Interestingly, 10/28 (36%) of carriers had a suggestively prolonged (QTc \geq 440 ms) interval in TOPMed, while 9/25 (36%) of carriers in the UK Biobank had such an interval.

Estimating the magnitude of effect of SCN5A pathogenic and likely pathogenic variants

Pathogenic and likely pathogenic variants in canonical LQTS genes (*KCNQ1*, *KCNH2*, *SCN5A*) from ClinVar were tested for association with QTc interval using collapsed tests. As expected *KCNQ1* and *KCNH2* were associated with significantly prolonged QTc intervals (**Supplemental Table VII**); however, pathogenic and likely pathogenic variants in *SCN5A* were not associated with the QTc interval across TOPMed, UK Biobank and MyCode ($P=0.26$). We further performed association tests between pathogenic and likely pathogenic *SCN5A* variants and the PR interval. Inverse-variance fixed-effects meta-analysis showed that the PR interval ($\beta=15.2$ ms; $P=3.09\times 10^{-5}$; N carriers=44) was significantly increased among carriers of such variants across TOPMed and UK Biobank (**Supplemental Tables VII and XIII, and Supplemental Figure IXA**). In MyCode, such *SCN5A* variants also were associated with marked PR prolongation, albeit with larger effect ($\beta=44.0$ ms; $P=1.20\times 10^{-7}$; N carriers=73) (**Supplemental Figure IXA**). Penetrance of deleterious *SCN5A* variants for PR conduction abnormalities was incomplete: In aggregate, 21% (6/28) of carriers of LOF, pathogenic and likely pathogenic variants in TOPMed had first-degree atrioventricular block (PR \geq 200 ms). In UK Biobank and MyCode, penetrance estimates were 19% (5/26) and 34% (30/89), respectively. Overall, LOF, pathogenic and likely pathogenic variants were carried by 0.1% of individuals, and were associated with a 5.6-fold increased odds of first-degree atrioventricular block across TOPMed and UK Biobank ($P=8.4\times 10^{-5}$) (**Supplemental Table XV and Supplemental Figure IXB**). In MyCode, such variants were associated with a 12.4-fold increased odds of first-degree atrioventricular block (**Supplemental Table XV and Supplemental Figure IXC**).

ClinVar phenotype reports for SCN5A pathogenic and likely pathogenic variants

While pathogenic and likely pathogenic *SCN5A* variants were not associated with QTc duration in the present analysis, *SCN5A* is well-described for LQTS. *SCN5A* variants are further known to cause a range of other conduction diseases, such as Brugada syndrome, a phenotype generally not associated with major QTc abnormalities.⁶⁴ It is possible that very few true QT prolonging, gain-of-function,¹¹ *SCN5A* variants were present in the datasets. In the current state of ClinVar, it is particularly difficult to parse out which variants are responsible for loss-of-function phenotypes and which are responsible for gain-of-function phenotypes, as very many were reported for both (**Supplemental Table XIII**). It is essential that clinical variants be interpreted within a context of phenotypes, especially when a gene has pleiotropic effects.

Description of TOPMed participating studies

Genetics of Cardiometabolic Health in the Amish: The Amish Complex Disease Research Program includes a set of large community-based studies focused largely on cardiometabolic health carried out in the Old Order Amish (OOA) community of Lancaster County, Pennsylvania. Over 7,500 Amish have been recruited to date. This Amish community is a founder population who immigrated to Pennsylvania from Western Europe in the early 1700's, later expanding into other regions of the U.S. The Amish cohort participating in the TOPMed Consortium comprises 1,120 subjects ≥ 18 years of age from large multigenerational families who were recruited for specific protocols between 2001 and 2006. Subjects have been extensively phenotyped for a range of cardiometabolic traits, including anthropometry, lipids, blood pressure, glucose and related measures, vascular imaging, and a range of other phenotypes. DNA samples were collected and serum and plasma samples biobanked. The TOPMed Program has provided whole genome sequencing data to complement GWAS array data already collected in >7,000 Amish study participants. Due to their ancestral history, the OOA are enriched for many variants that arose in the population from a single founder (or small number of founders) and propagated through genetic drift. The clinical examination included a supine 12-lead electrocardiogram (ECG), which was acquired with a GE Marquette digital recording system. The readings were processed by the Marquette computer system.

Atherosclerosis Risk in Communities: the Atherosclerosis Risk in Communities (ARIC) study is a prospective population-based study of 15,792 men and women 45 to 64 years of age at enrollment in 1987-89 (73% of European descent), recruited from four communities in the United States (suburbs of Minneapolis, Minnesota; Washington County, Maryland; Jackson, Mississippi; and Forsyth County, North Carolina) between 1987-1989 to investigate the epidemiology of cardiovascular disease. At baseline and four follow-up visits, participants underwent a standard supine 10-second 12-lead electrocardiogram using a MAC PC cardiograph (Marquette Electronics Inc, Milwaukee, WI). Electrocardiograms were transmitted to the ARIC ECG Reading Center for coding, interpretation and storage.

Cleveland Family Study - Whole genome sequencing Collaboration: The Cleveland Family Study (CFS) was designed to investigate the familial basis of sleep disordered breathing. The study consists of data collected from 2,284 individuals (46% African-American) from 361 families. Index probands (n=275) were recruited from 3 area hospital sleep labs if they had a confirmed diagnosis of sleep apnea and at least 2 first-degree relatives available to be studied. In the first 5 years of the study, neighborhood control probands (n=87) with at least 2 living relatives available for study were selected at random from a list provided by the index family and also studied. All available first-degree relatives and spouses of the case and control probands also were recruited. Second-degree relatives, including half-sibs, aunts, uncles and grandparents, were also included if they lived near the first-degree relatives (cases or controls), or if the family had been found to have two or more relatives with sleep apnea. Blood was sampled and DNA isolated for participants seen in the last two exam cycles. The sample, which is enriched with individuals with sleep apnea, also contains a high prevalence of individuals with sleep apnea-related traits, including obesity, impaired glucose tolerance, and hypertension.

Four visits occurred from 1990 - 2006, including a final visit from 2001 - 2006 at a General Clinical Research Center. The last three exams targeted all subjects who had been studied at earlier exams, as well as new minority families and family members of previously studied probands who had been unavailable at prior exams. ECG was collected on the final GCRC visit using a 12-lead MAC® 6 Cardiograph by trained research nurses the morning after an in-lab sleep study in a supine or semi-recumbent position. Electrocardiogram collection procedures are available at <https://sleepdata.org/datasets/cfs/pages/manuals/electrocardiogram>.

Cardiovascular Health Study: The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers (Sacramento, CA; Hagerstown, MD; Winston-Salem, NC; Pittsburgh, PA). The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888.

At the baseline visit, and during subsequent annual clinic visits, twelve-lead resting electrocardiograms (ECGs) were obtained on all participants using the MAC PC-DT ECG recorder (Marquette Electronics Inc., Milwaukee, WI). Paper copies were produced for review at the Field Center. Electrocardiographic data were stored electronically and transmitted daily to the ECG Reading Center for analysis using the Novacoder ECG measurement and classification system.

Blood samples were drawn from participants during annual clinic visits. DNA was subsequently extracted from available samples. CHS participants selected for inclusion in the TOPMed sequencing program included African-American participants, cases of idiopathic venous thromboembolism, myocardial infarction, coronary heart disease, or stroke along with a random sample of “healthy elderly”. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

Framingham Heart Study: The Framingham Heart Study is an observational study located in Framingham, Massachusetts initiated by the US Public Health Service in 1948 to examine the epidemiology and risk factors for cardiovascular disease. The study enrolled Framingham citizens in the Original cohort (n=5209), Offspring cohort – children of the Original cohort and their spouses (n=5124), and Third Generation cohort – adult children from the Offspring cohort (n=4095). Participants were examined every two (Original cohort) or four to eight years (Offspring and Third Generation cohorts) with standardized Framingham Heart Study examinations comprising a collection of data. At each examination, data on medical history, physical examination, and laboratory tests were collected. Regular health-status updates for cardiovascular disease included requests for hospital admission or outpatient records and ECGs. Digitized ECGs were performed using the Marquette (now General Electric, Fairfield, CT) MAC 5000. The digitally recorded ECGs were recorded at either 250 or 500 samples per second with a filter of 150Hz. They were printed on standard ECG paper at 25 mm/s and 0.1 mV/mm, followed by transformation for contemporary analysis by the MUSE 8 ECG Management System (General Electric, Fairfield, CT).

Jackson Heart Study: Between 2000 and 2004, JHS recruited 5,306 African American participants from the Jackson, Mississippi, metropolitan tri-county area (Hinds, Madison, and Rankin). JHS is a prospective, community-based cohort designed to investigate risk factors for cardiovascular disease among African Americans. A range of measures, including traditional and putative CVD risk factors, health behaviors, detailed demographic, socioeconomic and sociocultural factors, medication use, anthropometry, blood pressure, assessments of kidney function and diabetes, and biochemical analytes, were obtained at the baseline JHS examination and in two subsequent clinic visits (2005-2008 and 2009-2013). Biological samples (i.e., blood and urine) have been assayed for putative biochemical risk factors and stored for future research. DNA has been extracted and lymphocytes have been cryopreserved for studies of candidate genes, genome-wide scanning, whole genome sequencing, expression, and other -omics investigations. Supine 12-lead digital electrocardiograms (ECGs) were obtained in (Exams 1 and 3.). The ECGs were recorded after overnight fast and transmitted using the Marquette MAC/PC digital ECG recorder (Marquette Electronics, Milwaukee, Wisconsin) to the Electrocardiographic Reading Center at the University of Minnesota for Exam 1 ECGs. The Exam 1 ECGs were then read using a computer algorithm developed using the Minnesota Code Modular ECG Analysis System developed for clinical trials and population studies and have been validated previously.⁷ For Exam 3, a supine 12-lead ECG at rest was obtained for JHS participants using the GE MAC1200 (GE Healthcare, Jackson, Mississippi). An electrode locator was used to determine and standardize the positioning of chest electrodes. Digital ECG signals were sent through a phone modem to the JHS ECG reading center located at the Epidemiological Cardiology Research Center, Wake Forest University, Winston-Salem, North Carolina, where ECGs were automatically processed using 2001 GE Marquette 12-SL software after visual inspection for technical errors.

Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. The cohort is a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Approximately 38 percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian (predominantly of Chinese descent). Participants were recruited during 2000-2002 from 6 field centers across the U.S. (at Wake Forest University; Columbia University; Johns Hopkins University; the University of Minnesota; Northwestern University; and the University of California – Los Angeles). All underwent anthropomorphic measurement and extensive evaluation by questionnaires at baseline, followed by 4 subsequent examinations at intervals of approximately 2-4 years. Age and sex were self-reported. Further information can be found at:

http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000209.v13.p3 and
<http://www.mesa-nhlbi.org>.

ECGs were recorded in the supine position after a period of rest. MESA ECG data were collected using GE MAC 1200 electrocardiographs. Digitally collected ECGs were transferred via phone lines to the MESA ECG center (EPICARE). The ECGs were automatically processed by use of GE Marquette 12-SL software (2001 version), after visual inspection of the recordings

for quality. HRV measures were calculated from 3 sequential 10 second ECGs, and the average in these ECGs were used.

Women's Health Initiative:

Women's Health Initiative. The Women's Health Initiative (WHI) is a long-term national health study focused on heart disease, cancer, and osteoporotic fractures in older women. WHI originally enrolled 161,808 women aged 50-79 between 1993 and 1998 at 40 centers across the US, including both a clinical trial (including three trials for hormone therapy, dietary modification, and calcium/vitamin D) and an observational study arm. The recruitment goal of WHI was to include a socio-demographically diverse population with racial/ethnic minority groups proportionate to the total minority population of US women aged 50–79 years. This goal was achieved; a diverse population, including 26,045 (17%) women from minority populations, was recruited. Two WHI extension studies conducted additional follow-up.

The WHI contribution of TOPMed was designed as a case-control study of stroke and venous thromboembolism (VTE). Approximately 5,000 stroke and 1,000 VTE cases and 5,000 controls were selected for Whole genome sequencing. The controls were selected to frequency match the cases by age at recruitment, ethnicity, and membership in the WHI hormone therapy trial. Study protocols and consent forms were approved by the IRB at all participating institutions.

Standard 12-lead ECGs were recorded in all women by strictly standardized procedures in all clinical centers. Special attention was paid to locating the chest electrodes in precise positions.⁶All ECGs were processed in a central laboratory (EPICARE Center, Wake Forest University, Winston-Salem, NC), where they were visually inspected for technical errors and inadequate quality. ECGs were processed by the Marquette 12-SLprogram (GE Marquette).

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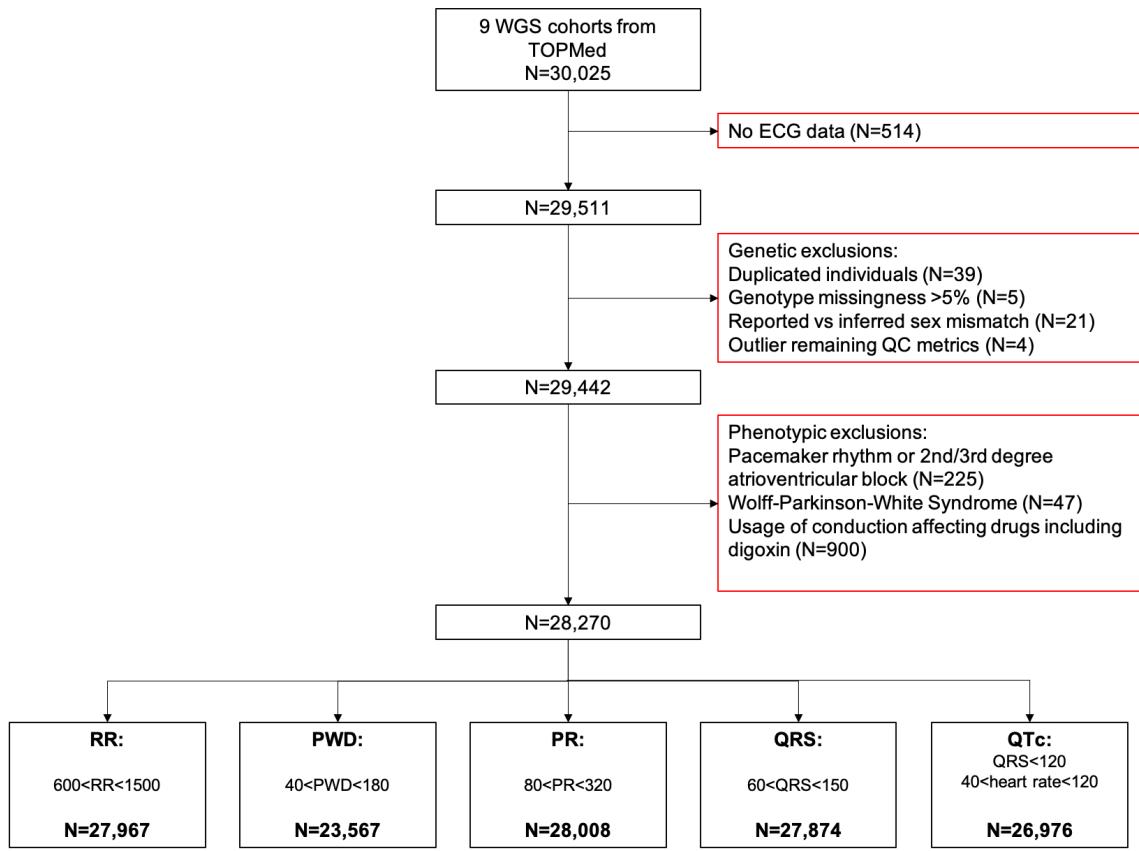
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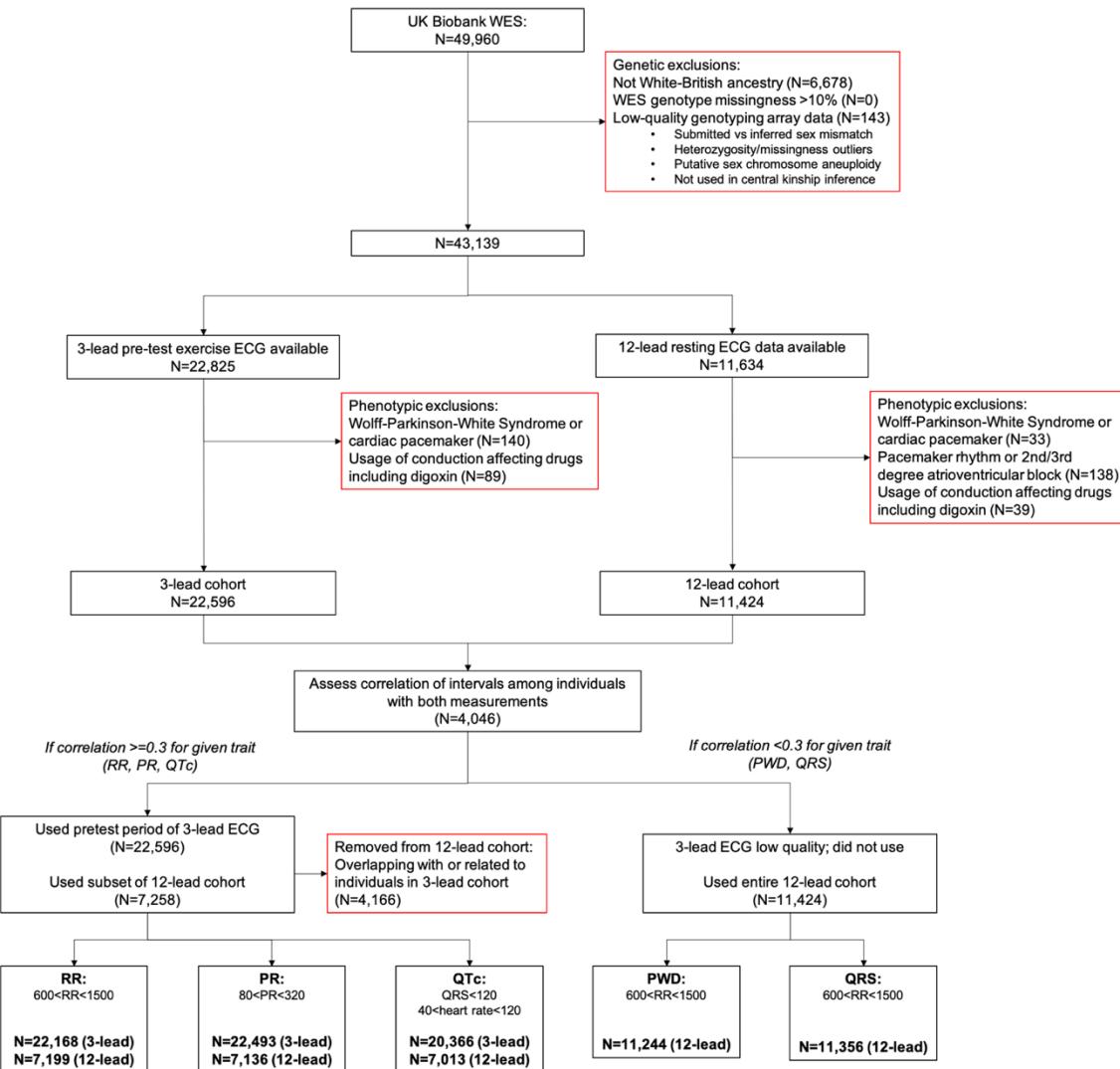
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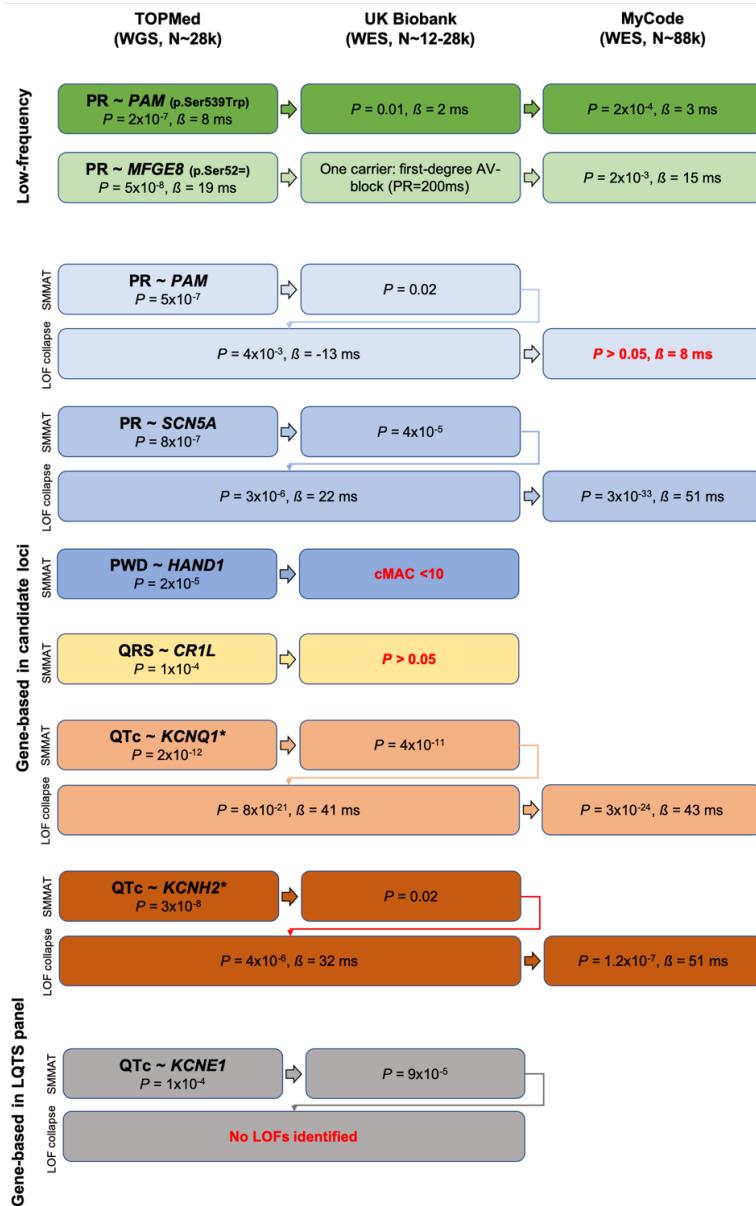
Supplemental Figures



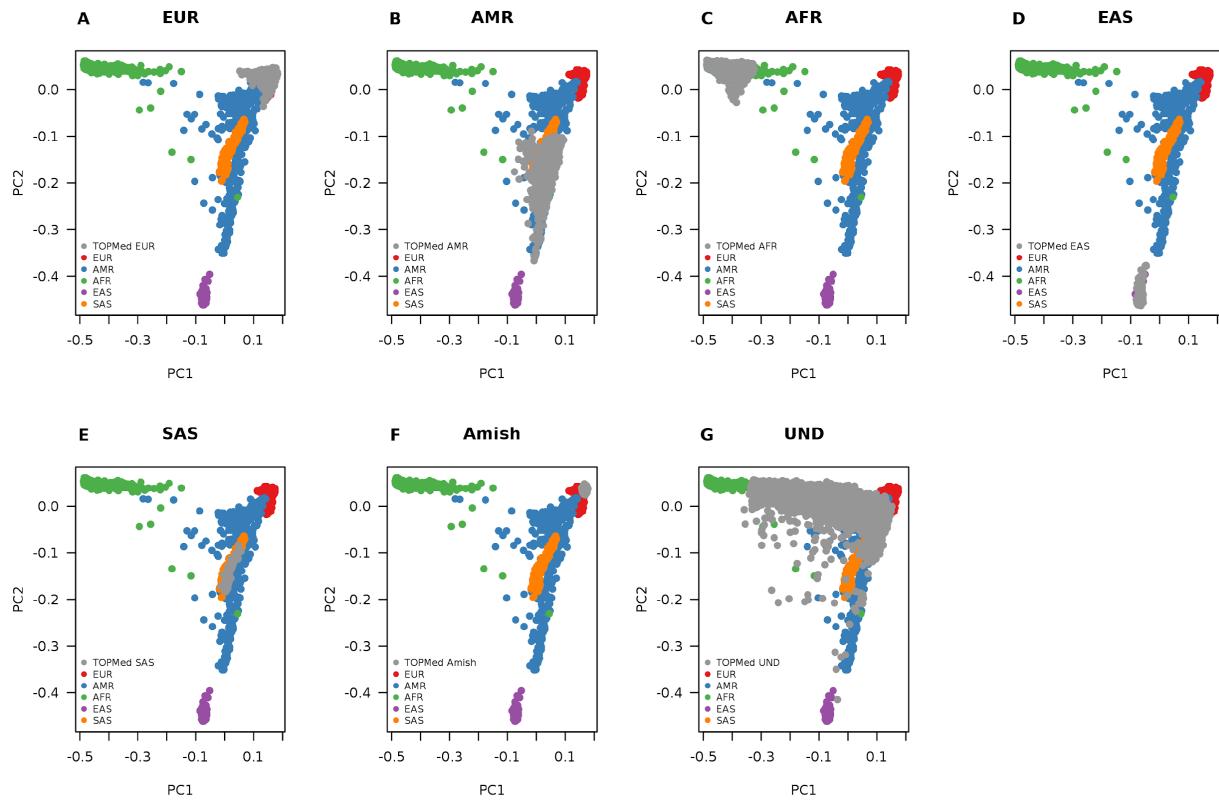
Supplemental Figure I. Sample selection including genetic and phenotypic exclusions for individuals in TOPMed. Genetic and Phenotypic exclusions in TOPMed yield between 23,567 and 28,008 individuals with whole genome sequencing data and ECG data for each trait after general and trait-specific exclusions. WGS, whole genome sequencing; ECG, electrocardiogram; RR, RR interval, PR, PR interval; PWD, P-wave duration; QRS, QRS complex duration; QTc, Bazett's-corrected QT interval.



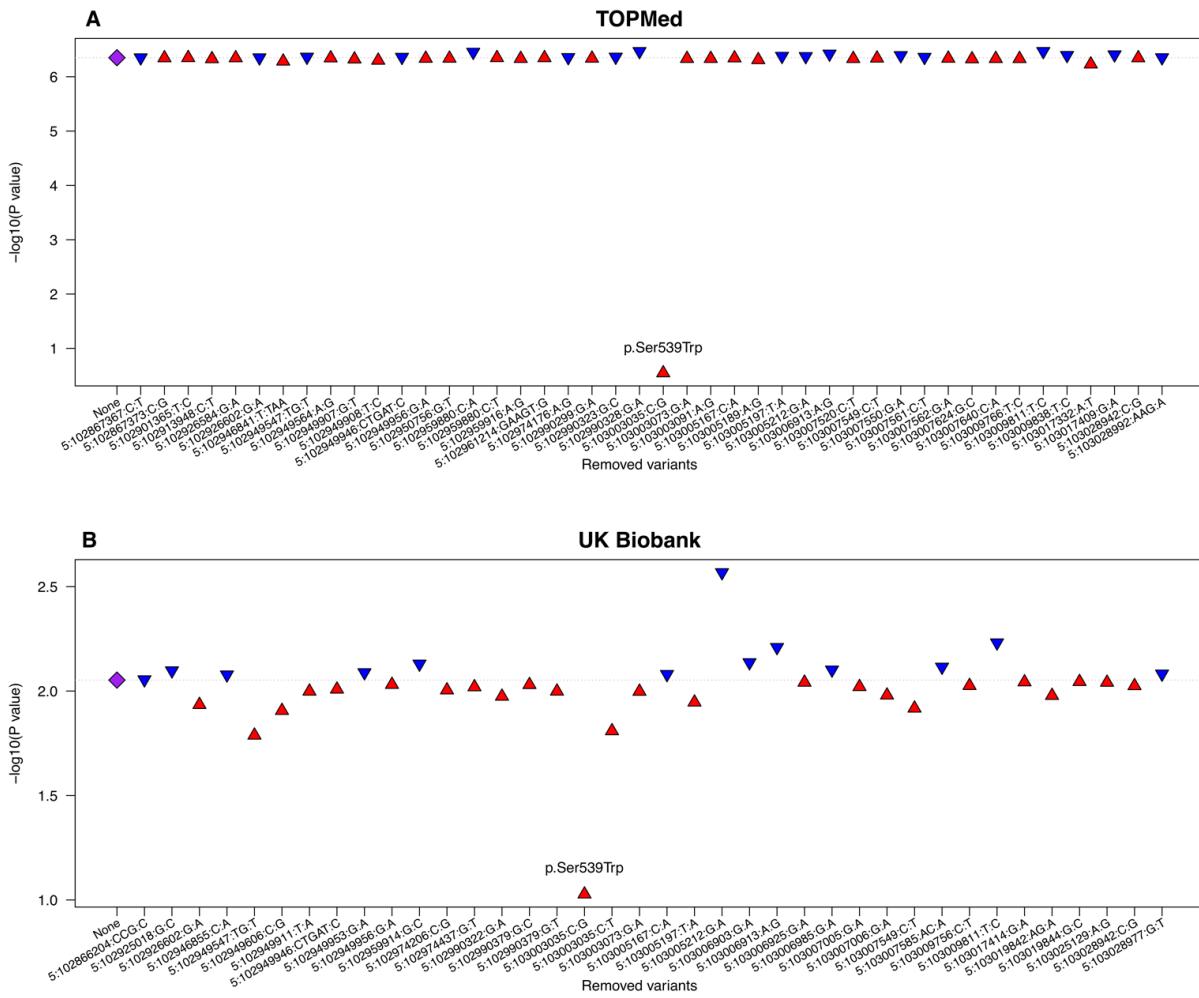
Supplemental Figure II. Sample selection flow for individuals included from the UK Biobank. The pretest period of the 3-lead exercise ECG and 12-lead resting ECG data were utilized for RR, PR, and QTc intervals. In all UK Biobank analyses these traits, results from both cohorts were combined using meta-analysis approaches. For PWD and QRS durations, because the correlations between two data sets were low, only the 12-lead resting ECG data were included in UK Biobank analyses of these traits. WES, whole exome sequencing; ECG, electrocardiogram; RR, RR interval, PR, PR interval; PWD, P-wave duration; QRS, QRS complex duration; QTc, Bazett's-corrected QT interval



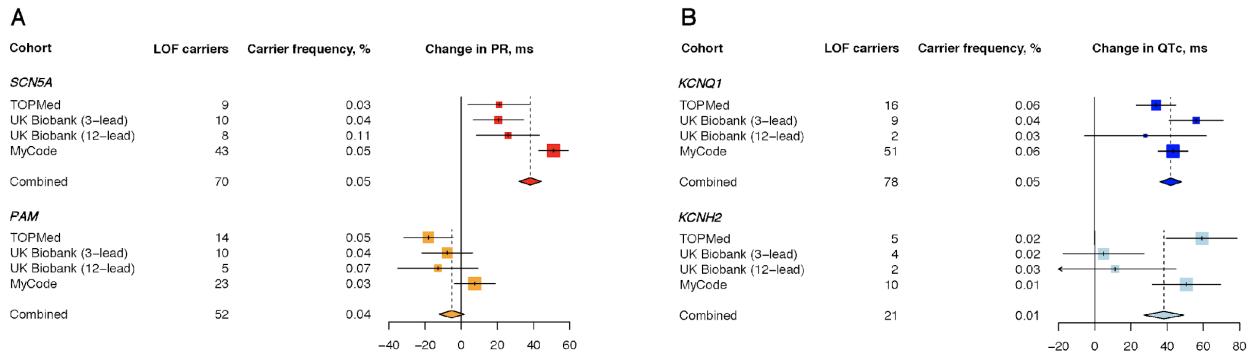
Supplemental Figure III. Flowchart for variant and gene discovery and replication. In primary discovery analyses for protein-coding low-frequency ($0.1\% < \text{MAF} < 1\%$) variants, we 1) identified variants significantly associated with a trait in TOPMed 2) attempted replication in UK Biobank and if there was evidence for the variant we 3) put it forward for additional replication in MyCode. In primary gene-based tests, we took a two-stage approach where we first utilized SMMAT tests for variants with $\text{MAF} < 1\%$ and then an LOF collapsing test for LOF variants with $\text{MAF} < 0.1\%$. We 1) identified significantly associated genes in TOPMed using SMMAT, 2) performed SMMAT in UK Biobank and if there was a nominal association we 3) performed LOF collapsing tests across TOPMed and UK Biobank; 4) we then replicated results from LOF collapsing tests in MyCode. * *KCNQ1* and *KCNH2* genes were also part of the LQTS panel. WGS, whole genome sequencing; WES, whole exome sequencing; SMMAT, Variant Set Mixed Model Association Tests; LOF, loss-of-function; LQTS, long-QT syndrome



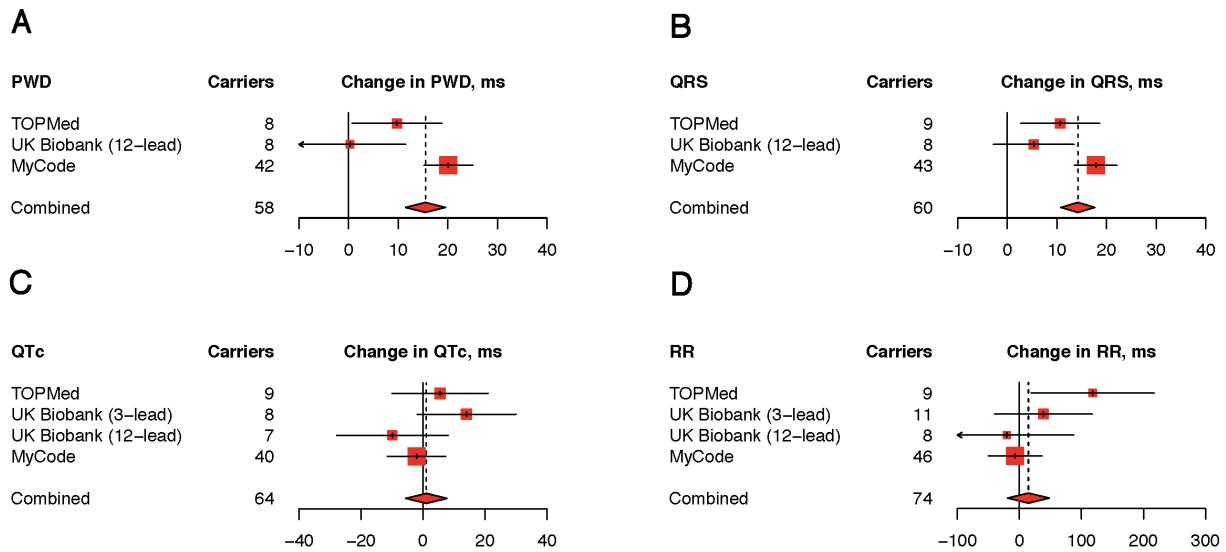
Supplemental Figure IV. Genetically determined ancestral groups in TOPMed participants. Panel A-E represents the genetically determined ancestral groups (European [EUR], Ad Mixed American [AMR], African [AFR], East Asian [EAS], South Asian [SAS]) from ADMIXTURE. Panel F and G shows self-reported Amish and genetically undermined population (UND). Grey dots represent TOPMed participants, and red, blue, green, purple, and orange dots show different ethnic groups from 1000G reference panel, respectively.



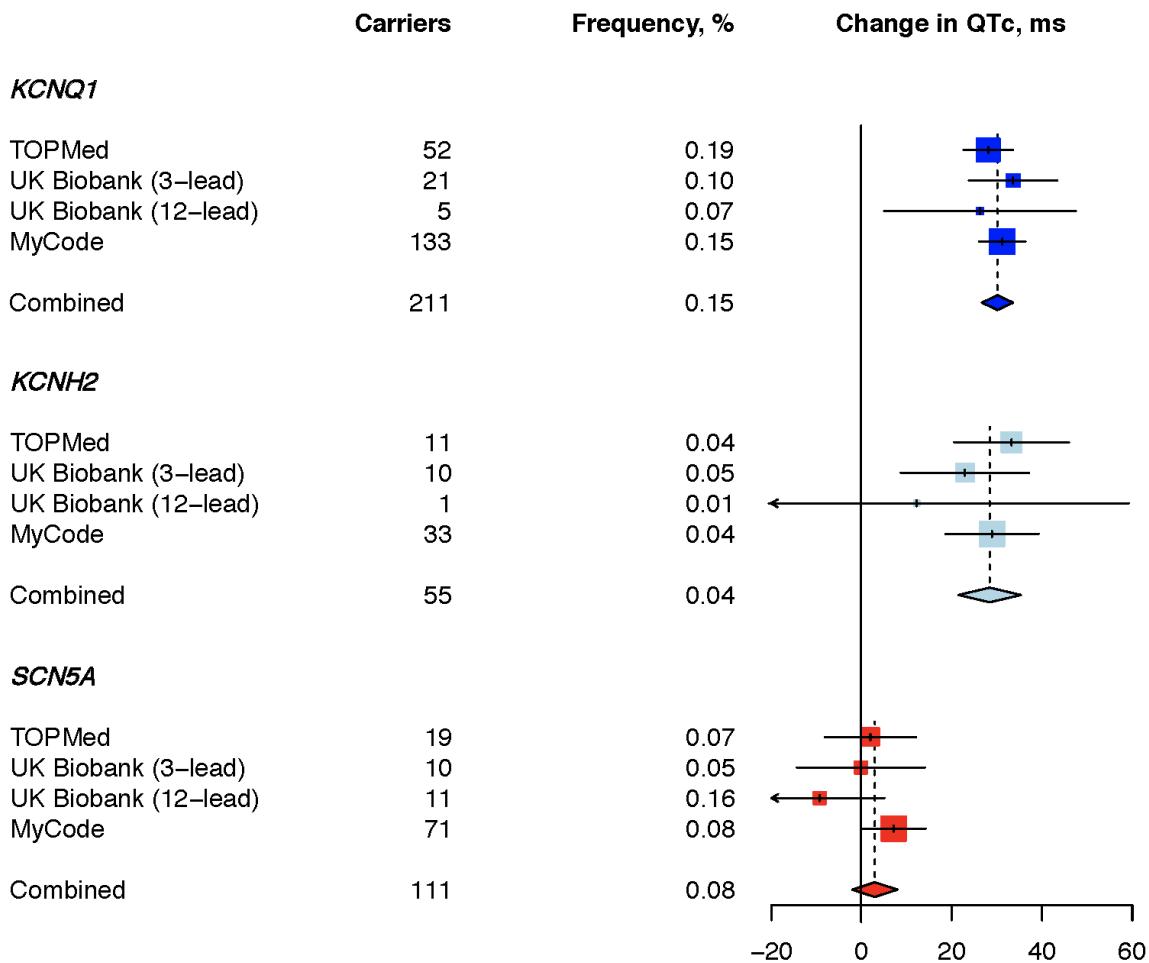
Supplemental Figure V. Association between variation in PAM and the PR interval is driven by coding variant at Ser539Trp. Panel A and B shows leave-one-variant-out association results for PAM from TOPMed and UK Biobank respectively. X-axis represent the removed variants and Y axis indicate association results between variation in PAM and the PR interval after removing one variant. The diamond purple dot is the original association result without removing any variants. The blue and red dots indicate the decreased and increased p-values, respectively. The leave-one-variant-out association results illustrate that the association between PAM and the PR interval was driven by p.Ser539Trp.



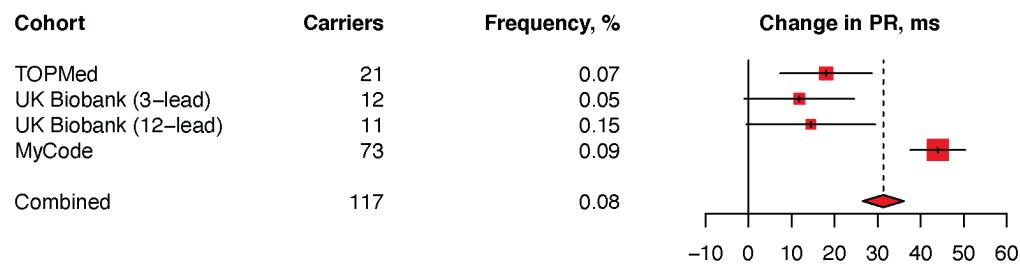
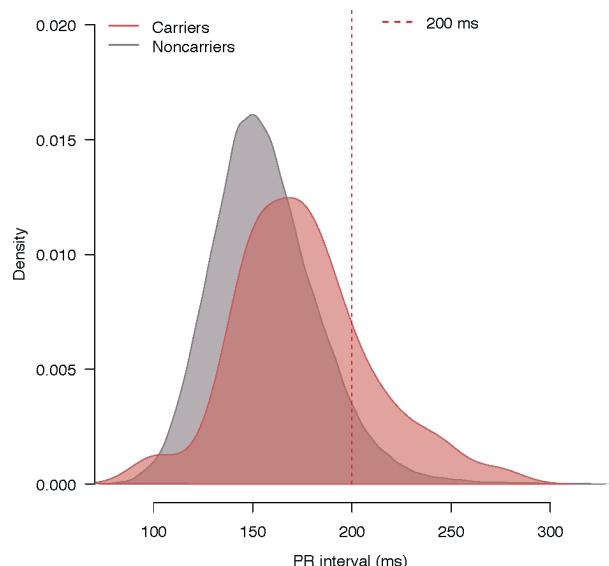
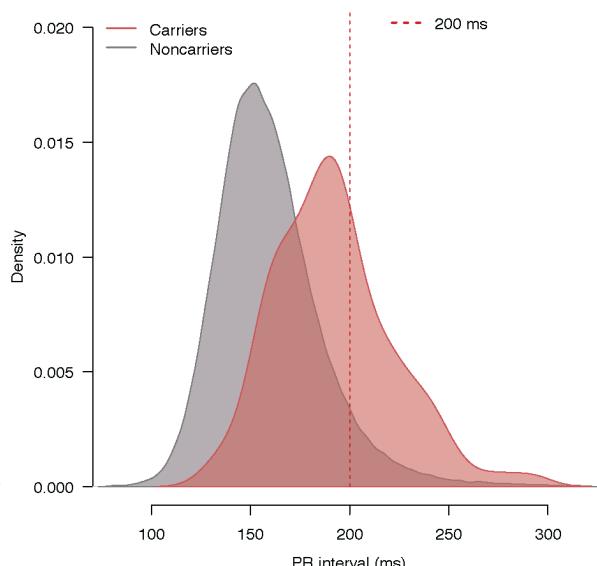
Supplemental Figure VI. Forest plots for rare loss-of-function (LOF) variants and their effects on ECG traits in TOPMed, UK Biobank, and MyCode. Figure 6A shows the effect of LOF variants in *SCN5A* and *PAM* on the PR interval, including an inverse-variance-weighted fixed-effects meta-analysis. LOF variants in *SCN5A* increased by 38 ms ($P = 4.3 \times 10^{-32}$) while LOF variants in *PAM* were not significant ($P = 0.14$). Figure 6B shows the effect of *KCNQ1* and *KCNH2* LOF variants on the QTc interval, including meta-analyzed effect estimate of 42 ms ($P = 3.88 \times 10^{-44}$) and 38.24 ms ($P = 8.53 \times 10^{-12}$) prolongation, respectively.



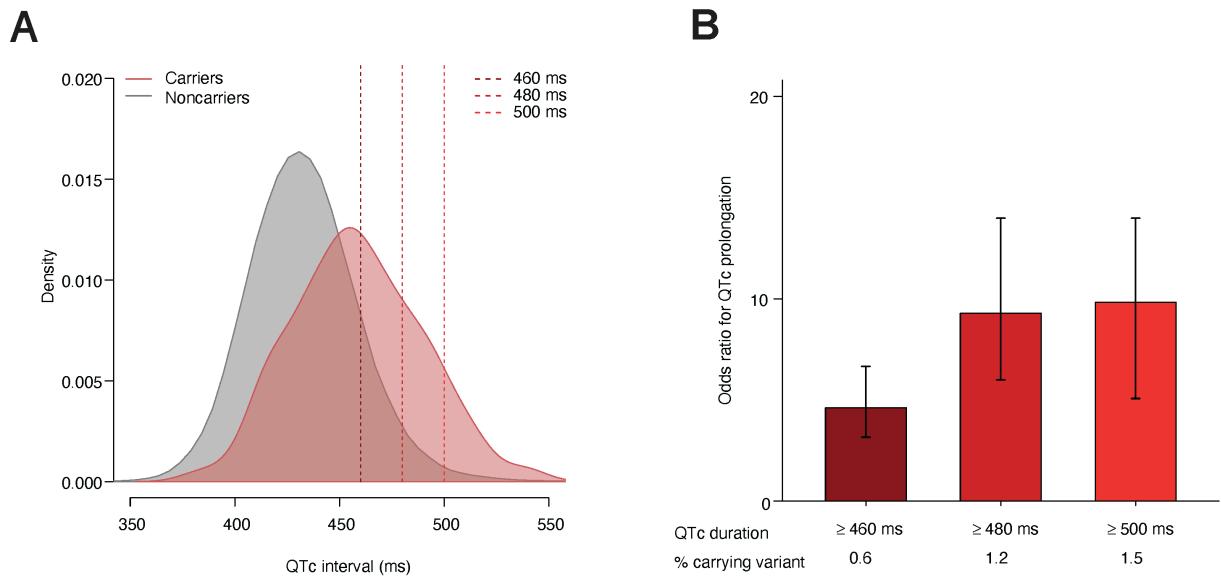
Supplemental Figure VII. Forest plots for rare *SCN5A* loss-of-function (LOF) variants and other ECG traits. Using inverse-variance weighted fixed-effects meta-analysis, *SCN5A* LOF variants were found to be associated with PWD and QRS duration. PWD, P-wave duration



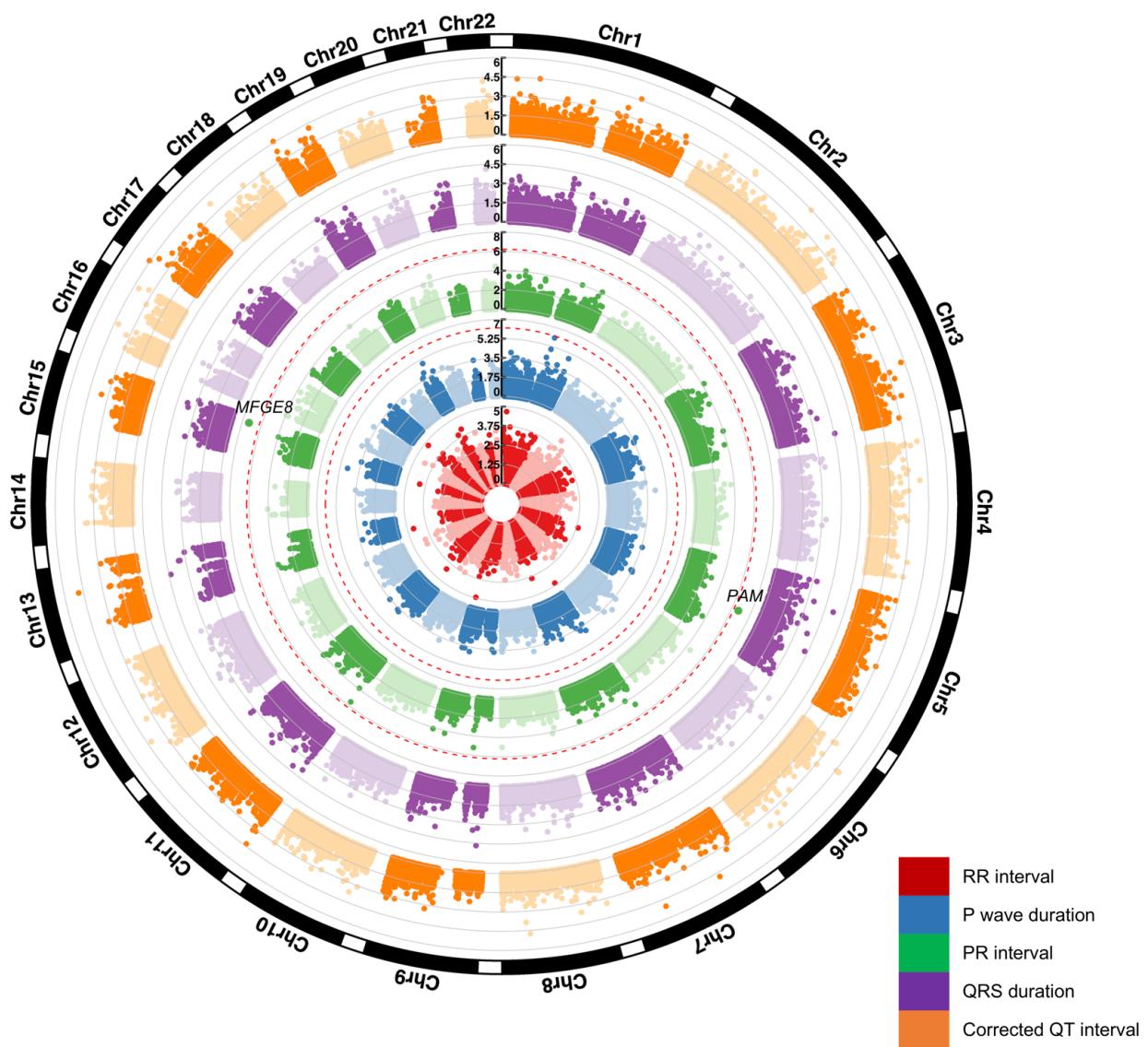
Supplemental Figure VIII. Effect of clinically-adjudicated pathogenic and likely pathogenic variants in *KCNQ1*, *KCNH2*, and *SCN5A* on QTc duration. Figure S8 shows inverse-variance weighted fixed-effects meta-analysis results of *KCNQ1*, *KCNH2*, and *SCN5A*. Carriers of a pathogenic or likely pathogenic variant in *KCNQ1* ($\beta = 30$ ms, $P = 7.0 \times 10^{-66}$) and *KCNH2* ($\beta = 29$ ms, $P = 7.2 \times 10^{-16}$) had significantly prolonged QTc intervals, whereas pathogenic or likely pathogenic variants in *SCN5A* were not associated.

A**B****C**

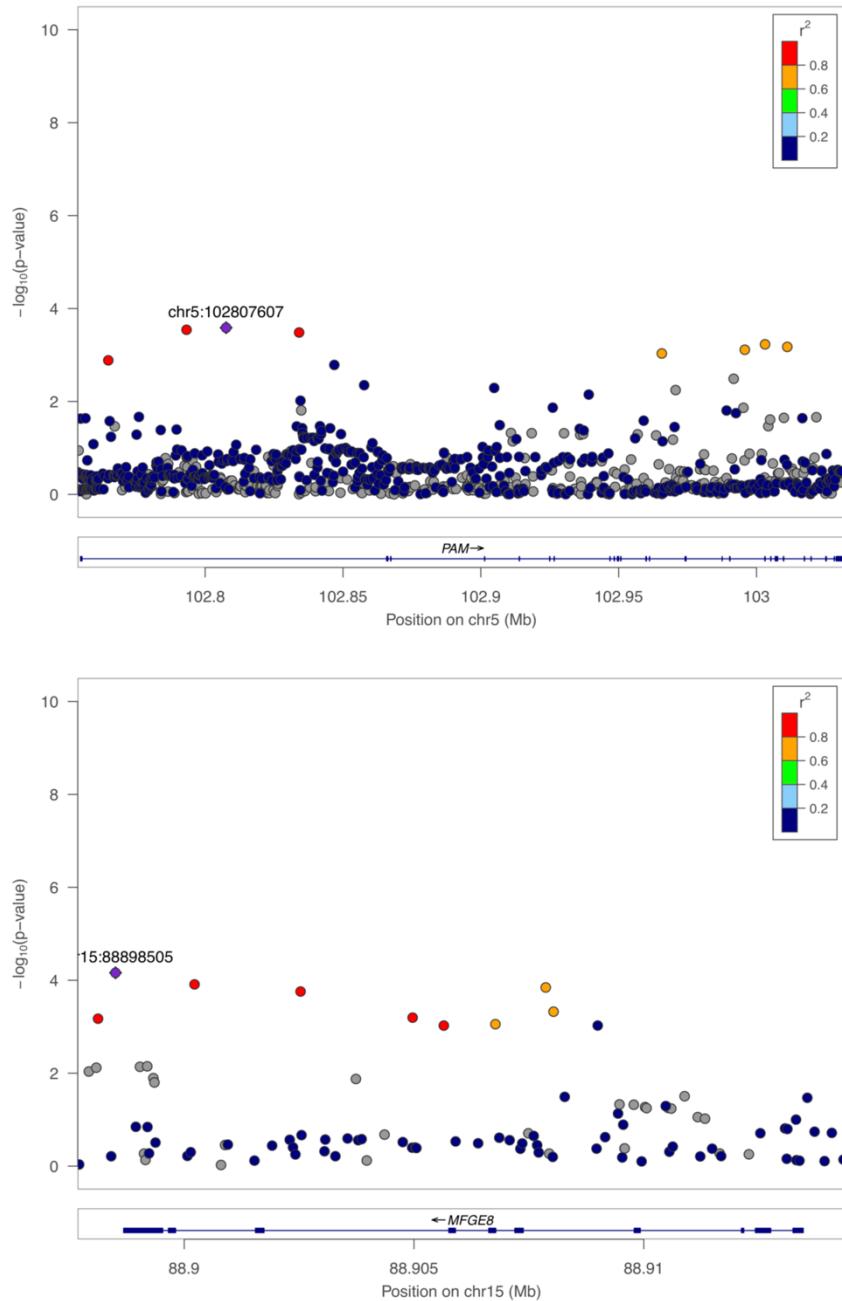
Supplemental Figure IX. Effect of pathogenic and likely pathogenic variants in SCN5A on PR interval. Panel A shows meta-analysis results of SCN5A. Carriers of a pathogenic or likely pathogenic variant in SCN5A had significantly prolonged PR intervals across TOPMed, UK Biobank and MyCode. Panel B illustrates the distribution of PR intervals among carriers of an LOF, pathogenic or likely pathogenic variant in SCN5A (red), as well as noncarriers in TOPMed and UK Biobank (grey). The dotted line represents the cutoff for 1st degree AV Block (QTc interval = 200 ms). Panel C illustrates the distribution of PR intervals among carriers of LOF, pathogenic or likely pathogenic variants in SCN5A, as well as noncarriers in MyCode.



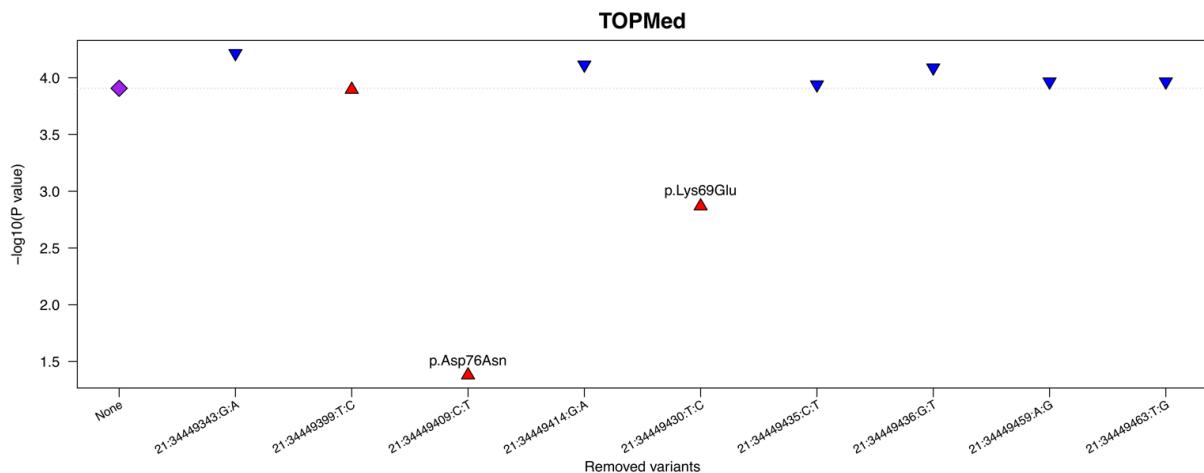
Supplemental Figure X. Effect of LOF, pathogenic or likely pathogenic variants in KCNQ1 and KCNH2 on QTc duration in MyCode. Panel A illustrates distributions for carriers (red, N = 181) of an LOF or pathogenic or likely pathogenic variant in KCNQ1, KCNH2 and noncarriers (grey, N = 88,085). The dotted lines represent QTc cutoffs of 460, 480 and 500 ms. Of the carriers, 44 (24.3%) individuals had QTc interval ≥ 480 ms while 3667 (4.2%) of noncarriers revealed QT prolongation. Panel B illustrates the odds ratio for QTc prolongation at different cutoffs (460, 480 and 500 ms) conferred by LOF, pathogenic or likely pathogenic variants in KCNQ1 and KCNH2 among unrelated participants. LOF, loss-of-function



Supplemental Figure XI. Association results of low frequency coding variant for ECG traits in TOPMed. Supplemental Figure XI illustrates circular Manhattan plot illustrating genome-wide association testing results between five ECG traits and low frequency variants with minor allele frequency (MAF) between 0.1% and 1% in TOPMed. The variants that reached to a Bonferroni threshold (**Supplemental Methods**, red dotted lines) are annotated with the genes.



Supplemental Figure XII. Regional association results of common variants at two identified genes from low frequency variant analysis for PR interval. Regional plots of common variants for PR interval at *PAM* and *MFGE8* in TOPMed. These two genes were identified from low frequency variant analysis. The most significant variant at each locus is plotted with diamond shape. Colors of dots represent the degree of linkage disequilibrium (r^2) to the top variant. The lower part of each panel shows the locations of genes at the respective loci. r^2 , degree of linkage disequilibrium; chr, chromosome; Mb, megabases; cM, centiMorgan. Regional plots were created using LocusZoom.



Supplemental Figure XIII. Association between predicted-deleterious variants in *KCNE1* and the QTc interval is driven by coding variants p.Asp76Asn and p.Lys69Glu in TOPMed. This figure shows leave-one-variant-out association results for *KCNE1* from TOPMed. X-axis represent the removed variants and Y axis indicate association results between rare variation in *KCNE1* and the QTc interval after removing one variant. The diamond purple dot is the original association result without removing any variants. The blue and red dots indicate the decreased and increased p-values, respectively. The leave-one-variant-out association results illustrate that the association between *KCNE1* and the QTc interval was driven by p.Asp76Asn and p.Lys69Glu.

Supplemental Tables

Supplemental Table I. Characteristics of TOPMed participants stratified by ancestry

Ancestral group	RR interval						
	AFR	AMR	Amish	EAS	EUR	SAS	UND
No. Participants	5034	615	1028	727	16749	56	3758
Female (%); N	0.66;3342	0.56;347	0.49;504	0.56;410	0.65;10956	0.211	0.67;2507
Mean age at ECG (years); SD	56.83;13.14	60;9.92	48.86;16.05	61.51;9.93	61.88;11.61	60.56;9.64	59.97;12.98
Mean Interval length (ms); SD	934.44;155.01	967.73;146.31	959.61;140.98	963.23;131.4	940.19;145.99	936.98;156.94	916.46;156.18
Mean height (cm); SD	167.8;9.49	160.69;8.47	166.13;8.79	161.05;8.73	166.14;9.45	165.99;7.6	165.04;9.9
Mean weight (kg); SD	88.56;21.07	77.13;14.08	74.37;13.27	63.26;11.26	77.38;17.22	73.09;18.49	82.77;20.29
Myocardial Infraction (%); cases/total samples	0.1;463/4486	0.08;44/528	0.02;16/1026	0.03;22/702	0.1;1642/16210	1;12/12	0.12;322/2693
Heart failure (%); cases/total samples	0.09;384/4240	0.05;29/528	0;0/0	0.03;21/702	0.07;1149/15790	1;7/7	0.13;335/2598
Beta blocker (%); cases/total samples	0.12;600/4962	0.09;55/615	0.02;20/1028	0.1;74/727	0.14;2267/16740	0.5;28/56	0.16;607/3735
Calcium Channel Blocker (%); cases/total samples	0.22;981/4523	0.08;50/615	0;5/1028	0.12;84/727	0.09;1423/16740	0.27;15/56	0.18;662/3635
PWD							
Ancestral group	AFR	AMR	Amish	EAS	EUR	SAS	UND
No. Participants	4149	520	-	700	15801	-	2397
Female (%); N	0.66;2743	0.55;286	-	0.57;398	0.67;10564	-	0.66;1575
Mean age at ECG (years); SD	57.66;12.01	60.17;9.22	-	61.68;9.87	61.94;11.16	-	61.04;10.78
Mean Interval length (ms); SD	115.07;13.14	106.76;12.55	-	103.01;12.36	108.15;12.97	-	111.37;13.44
Mean height (cm); SD	167.97;9.28	161.01;8.53	-	160.96;8.71	165.95;9.35	-	166.02;9.54
Mean weight (kg); SD	88.59;20.26	77.49;14.22	-	63.19;11.12	77.03;16.81	-	83.08;19.16
Myocardial Infraction (%); cases/total samples	0.1;396/4149	0.07;35/520	-	0.03;21/700	0.1;1548/15799	-	0.07;158/2396
Heart failure (%); cases/total samples	0.08;319/4127	0.04;19/520	-	0.03;20/700	0.07;1062/15618	-	0.06;138/2391
Beta blocker (%); cases/total samples	0.1;411/4077	0.07;34/520	-	0.1;69/700	0.13;2009/15792	-	0.09;217/2374
Calcium Channel Blocker (%); cases/total samples	0.22;795/3644	0.08;42/520	-	0.11;79/700	0.08;1308/15792	-	0.18;408/2275
PR interval							
Ancestral group	AFR	AMR	Amish	EAS	EUR	SAS	UND
No. Participants	5063	616	1024	727	16707	57	3814
Female (%); N	0.66;3366	0.57;351	0.49;504	0.57;411	0.66;10950	0.19;11	0.67;2547
Mean age at ECG (years); SD	56.74;13.1	59.98;9.91	48.77;15.95	61.52;9.92	61.78;11.58	60.39;9.63	59.72;13.01
Mean Interval length (ms); SD	169.68;26.78	160.58;22.02	166.08;24.79	164.43;22.4	163.67;25.88	167.82;25.39	164.2;26.63
Mean height (cm); SD	167.78;9.5	160.67;8.48	166.1;8.8	161.03;8.72	166.12;9.44	166.02;7.52	165.01;9.96
Mean weight (kg); SD	88.6;21.18	77.05;14.12	74.37;13.3	63.2;11.24	77.34;17.2	73.32;18.2	82.71;20.31
Myocardial Infraction (%); cases/total samples	0.1;459/4469	0.09;46/532	0.01;15/1022	0.03;22/701	0.1;1628/16158	1;12/12	0.12;321/2697
Heart failure (%); cases/total samples	0.09;389/4228	0.05;26/527	0;0/0	0.03;21/701	0.07;1138/15732	1;8/8	0.13;332/2602
Beta blocker (%); cases/total samples	0.12;606/4991	0.09;54/616	0.02;19/1024	0.1;75/727	0.13;2234/16698	0.49;28/57	0.16;610/3791
Calcium Channel Blocker (%); cases/total samples	0.22;981/4556	0.08;50/616	0;5/1024	0.12;84/727	0.08;1403/16698	0.26;15/57	0.18;665/3691
QRS interval							
Ancestral group	AFR	AMR	Amish	EAS	EUR	SAS	UND
No. Participants	5019	610	1025	727	16644	57	3792
Female (%); N	0.66;3337	0.55;286	0.49;503	0.57;411	0.66;10930	0.19;11	0.67;2528
Mean age at ECG (years); SD	56.71;13.1	59.93;9.94	48.81;16.03	61.47;9.91	61.78;11.61	60.39;9.63	59.7;13.05
Mean Interval length (ms); SD	91.13;12.41	91.64;11.92	94.55;11.89	89.69;11.2	90.95;12.75	93.16;13.78	90.1;13.35
Mean height (cm); SD	167.77;9.46	160.6;8.5	166.15;8.77	161.03;8.73	166.12;9.45	166.02;7.52	165.04;9.94
Mean weight (kg); SD	88.56;21.22	76.97;14.16	74.36;13.3	63.3;11.31	77.36;17.25	73.32;18.2	82.73;20.26
Myocardial Infraction (%); cases/total samples	0.1;453/4426	0.09;46/527	0.01;15/1023	0.03;21/701	0.1;1630/16087	1;12/12	0.12;316/2664
Heart failure (%); cases/total samples	0.09;380/4188	0.05;28/524	0;0/0	0.03;21/701	0.07;1138/15661	1;8/8	0.13;338/2576
Beta blocker (%); cases/total samples	0.12;598/4947	0.09;55/610	0.02;20/1025	0.1;75/727	0.13;2243/16636	0.49;28/57	0.16;619/3769
Calcium Channel Blocker (%); cases/total samples	0.21;970/4512	0.08;48/610	0;5/1025	0.12;85/727	0.08;1414/16636	0.26;15/57	0.18;661/3670
QTc							
Ancestral group	AFR	AMR	Amish	EAS	EUR	SAS	UND
No. Participants	4887	596	998	715	16074	53	3653
Female (%); N	0.67;3272	0.58;344	0.5499	0.57;407	0.66;10654	0.21;11	0.67;2457
Mean age at ECG (years); SD	56.53;13.1	59.73;9.9	48.65;15.9	61.37;9.9	61.52;11.58	60.13;9.64	59.39;13.01
Mean Interval length (ms); SD	424.61;25.92	419.37;21.08	420.74;19.72	418.95;21.31	423.77;21.41	427.79;25.31	425.08;25.83
Mean height (cm); SD	167.7;9.45	160.51;8.47	166.04;8.75	160.97;8.75	166.08;9.43	166.12;7.74	165.98;9.88
Mean weight (kg); SD	88.53;21.3	76.78;14.19	74.28;13.17	63.27;11.32	77.32;17.22	73.09;18.49	82.74;20.27
Myocardial Infraction (%); cases/total samples	0.1;424/4321	0.09;44/516	0.02;15/996	0.03;20/690	0.1;1547/15555	1;12/12	0.12;299/2579

Heart failure (%); cases/total samples	0.09;354/4087	0.05;25/511	0;0/0	0.03;20/690	0.07;1073/15129	1;7/7	0.12;309/2486
Beta blocker (%); cases/total samples	0.12;570/4817	0.08;50/596	0.02;19/998	0.1;73/715	0.13;2108/16066	0.51;27/53	0.16;568/3630
Calcium Channel Blocker (%); cases/total samples	0.21;941/4387	0.08;45/596	0.01;5/998	0.12;84/715	0.08;1330/16066	0.26;14/53	0.18;624/3531

Note: AFR, African; AMR, Admixed American; EAS, East Asian; EUR, European; SAS, South Asian; UND, undetermined; ECG, electrocardiogram; SD, standard deviation; PWD, P-wave duration; QTc, Bazett-corrected QT

Supplemental Table II. Characteristics of UK Biobank participants with ECG

ECG Trait	RR	PWD	PR	QRS	QTc	
ECG measurement	12-lead	3-lead	12-lead	3-lead	12-lead	3-lead
No. Participants	7,199	22,168	11,244	7,136	22,493	11,356
Female (%), N	53;3,849	52;11,449	52;5,835	53;3,806	52;11,586	51;5,893
Age at ECG, mean (years), SD	62.05;7.58	52.82;5.56	62.34;7.50	62.04;7.57	52.81;5.56	62.32;7.50
Interval mean length (ms), SD	99.56;159.90	87.66;140.13	96.89;16.36	162.31;26.34	144.20;23.86	88.32;12.51
Myocardial Infarction (%), cases/ total samples	1.83; 13277,199	2.44; 541/22,168	1.75; 197/11,244	1.82; 13077,136	2.43; 546/22,493	1.75; 199/11,356
Heart Failure (%), cases/ total samples	0.47; 3477,199	0.81; 180/22,168	0.44; 49/11,244	0.48; 3477,136	0.81; 183/22,493	0.43; 49/11,356
Beta Blocker (%), Users / total samples	5.70; 4107,199	5.66; 1,254/22,168	5.64; 634/11,244	5.66; 40477,136	5.65; 1,271/22,493	5.63; 639/11,356
Calcium Channel Blocker (%), Users / total samples	9.03; 6507,199	6.77; 1,501/22,168	8.81; 99/11,244	9.00; 64277,136	6.90; 1,553/22,493	8.80; 999/11,356

Note: ECG, electrocardiogram; PWD, P-wave duration; QTc, Bazett-corrected QT; SD, standard deviation; 12-lead, resting ECG; 3-lead, pre-exercise stage ECG.

Supplemental Table III. Characteristics of Geisinger MyCode participants with ECG

ECG Trait	RR	PWD	PR	QRS	QTc
ECG measurement	12-lead	12-lead	12-lead	12-lead	12-lead
No. Participants	88,045	84,785	84,583	86,587	88,266
Female (%), N	60.04;52,858	60.91;51,640	60.92;51,532	60.61;52,477	61.73;54,486
Age at ECG, mean (years), SD	57.04;16.56	56.34;16.35	56.33;16.35	56.82;16.54	55.9;16.62
Interval mean length (ms), SD	860.23;153.4	104.97;15.57	159.61;26.9	90.69;14.57	433;28.12
Myocardial Infarction (%), cases/ total samples	7.43; 6,545/88,045	6.98; 5,921/84,785	6.97; 5,897/84,583	7.18; 6,217/86,587	6.7;5; 914/88,266
Heart Failure (%), cases/ total samples	7.03; 6,190/88,045	5.69; 4,822/84,785	5.68; 4,802/84,583	6.53; 5,653/86,587	5.96; 5,257/88,266
Beta Blocker (%), Users / total samples	22.01; 19,376/88,045	20.94; 17,755/84,785	20.88; 17,665/84,583	21.62; 18,723/86,587	20.6; 18,179/88,266
Calcium Channel Blocker (%), Users / total samples	10.55; 9,293/88,045	10.12; 8,583/84,785	10.1; 8,540/84,583	10.46; 9,055/86,587	10.14; 8,949/88,266

Note: ECG, electrocardiogram; PWD, maximum P wave duration; QTc, Bazett-corrected QT; SD, standard deviation;

Supplemental Table VI. Genome-wide significant common variants (MAF>1%) in TOPMed

ECG trait	Chr	Pos	Ref	Alt	Nearby gene	Freq, %	Beta, ms	P value
RR	1	207855718	C	T	<i>CD46</i>	8.7	-13.74	3.74E-10
	4	148255609	C	T	<i>NR3C2</i>	18.4	8.88	2.58E-08
	6	121793305	A	G	<i>GJA1</i>	21.3	-14.1	2.36E-16
	12	24631205	G	A	<i>SOX5</i>	12.2	11.34	2.07E-09
	14	23392602	A	G	<i>MYH6</i>	42.9	-10.42	1.43E-15
	20	38187703	A	G	<i>KIAA1755</i>	54.1	6.98	2.12E-08
PWD	3	38582762	T	C	<i>SCN5A-10A</i>	62.5	1.27	1.10E-24
	4	110778675	C	T	<i>PITX2</i>	26.4	-0.82	1.20E-09
	5	45952814	C	T	<i>HCN1</i>	30.4	0.77	4.86E-10
	7	116513961	T	G	<i>CAV1-2</i>	35.7	0.67	3.45E-08
	10	73650119	C	T	<i>SYNP02L</i>	19.4	1	2.86E-11
	12	114355435	C	T	<i>TBX5</i>	68.5	-0.82	6.17E-11
PR	1	2212668	A	G	<i>SKI</i>	88.7	2.23	3.35E-11
	2	8592946	C	T	<i>ID2</i>	48.6	-1.51	1.76E-11
	2	66534559	GT	G	<i>MEIS1</i>	60.9	-1.67	5.52E-14
	2	102782784	T	C	<i>TMEM182</i>	54.8	1.29	4.73E-09
	3	38725824	T	C	<i>SCN5A-10A</i>	66.5	-4.19	1.03E-74
	4	85741902	A	T	<i>AHGP24</i>	54.3	2.08	1.24E-17
PR	5	1095894	C	T	<i>SLC12A7</i>	31.8	1.35	2.45E-08
	5	173056020	A	C	<i>CREB2R</i>	66.8	1.49	6.17E-11
	7	35337797	G	A	<i>TBX20</i>	23.3	-1.42	1.72E-08
	7	116551247	C	A	<i>CAV1-2</i>	53.4	-2.23	4.25E-24
	10	103764323	C	T	<i>SHCPXD1A</i>	45.3	1.28	2.18E-09
	12	24605546	G	A	<i>SOX5</i>	12.1	-3.01	2.71E-20
QRS	12	114362169	G	A	<i>TBX5-3</i>	72	-1.99	4.00E-17
	13	21531367	T	A	<i>MICU2</i>	33.6	-1.52	5.79E-11
	1	61429585	C	A	<i>NFIA</i>	43	-0.61	8.15E-09
	3	38582762	T	C	<i>SCN5A-10A</i>	61.5	1.06	2.02E-22
	5	154491510	C	T	<i>HAN1</i>	40.5	-0.71	1.32E-11
	6	36679512	G	A	<i>CDKN1A</i>	19.6	0.99	1.50E-14
QTc	6	126733443	C	T	<i>CENPW</i>	50.6	-0.59	2.06E-08
	7	35466100	C	G	<i>TBX20</i>	1.7	2.26	6.04E-09
	7	116586368	G	A	<i>CAV1</i>	59.4	-0.62	9.95E-09
	10	112697341	A	G	<i>VTI1A</i>	41.2	0.76	3.83E-11
	18	44860589	A	T	<i>SETBP1</i>	34.7	-0.67	5.37E-10
	20	40487728	T	A	<i>MAFB</i>	1.57	2.28	3.06E-08
QTc	1	6219310	G	C	<i>RNF207</i>	20.8	1.93	3.06E-16
	1	162054452	C	T	<i>NOS1AP</i>	22.1	3.15	1.48E-43
	1	169104150	G	A	<i>NME7</i>	16.4	-1.97	1.97E-13
	3	38582762	T	C	<i>SCN5A</i>	61.5	-1.38	1.48E-11
	7	150947306	C	T	<i>KCNH2</i>	27.3	2.06	8.15E-21
	11	2463573	T	C	<i>KCNQ1</i>	94.1	4.56	7.47E-31
QTc	16	11597897	T	C	<i>LITAF</i>	50.9	-1.41	1.03E-13
	16	58515300	G	C	<i>CNOT1</i>	23.8	-1.88	3.82E-17
	17	70497327	GA	G	<i>KCNJ1</i>	34	-1.5	7.01E-14

Note, Chr: chromosome, Pos: Position, Ref: Reference allele, Alt: Alternative allele, Freq: Alternative allele Frequency; PWD, P-wave duration; QTc, Bazett-corrected QT interval

Supplemental Table V. Significant low-frequency variant (0.1%<MAF<1%) associations for PR interval in TOPMed and replication in UK Biobank and MyCode

ECG trait	rsID	Chr	Pos	Ref	Alt	Gene	MAF, %	Beta, ms	95% CI	P-value
TOPMed										
PR	rs78408340	5	103003035	C	G	PAM	0.47	7.96	[4.96, 10.95]	1.90x10 ⁻⁷
	rs141997845	15	88909841	C	T	MFGE8	0.1	18.69	[11.97, 25.40]	4.94x10 ⁻⁸
3-lead UK Biobank										
PR	rs78408340	5	103003035	C	G	PAM	1.07	2.06	[0.01, 4.11]	0.048
	rs141997845	15	88909841	C	T	MFGE8	-	-	-	-
12-lead UK Biobank										
PR	rs78408340	5	103003035	C	G	PAM	1.08	3.33	[-0.6, 7.26]	0.096
	rs141997845	15	88909841	C	T	MFGE8	-	-	-	-
meta UK Biobank										
PR	rs78408340	5	103003035	C	G	PAM	2.33	[0.51, 4.16]	0.012	
	rs141997845	15	88909841	C	T	MFGE8	-	-	-	-
MyCode										
PR	rs78408340	5	103003035	C	G	PAM	1.2	3.29	[1.57, 5.02]	1.80E-04
	rs141997845	15	88909841	C	T	MFGE8	0.043	14.65	[5.58, 23.74]	1.60E-03

Note: MAF, minor allele frequency; Chr, chromosome; Pos, position; Ref, reference allele; Alt, alternative allele; CI, confidence interval; meta, meta-analysis

Supplemental Table VI. Results from gene-based testing at candidate loci in TOPMed and replication in UK Biobank

ECG	Gene	TOPMed			3-lead UK Biobank			12-lead UK Biobank			meta UK Biobank		
		N	Variants	cMAC	P-value	N	Variants	cMAC	P-value	N	Variants	cMAC	P-value
	<i>MYH6</i>	27,967	204	897	0.001	-	-	-	-	-	-	-	-
	<i>TBX5</i>	27,967	26	287	0.002	-	-	-	-	-	-	-	-
RR	<i>ARHGAP24</i>	27,967	31	143	0.010	-	-	-	-	-	-	-	-
	<i>BNIP1</i>	27,967	16	56	0.014	-	-	-	-	-	-	-	-
	<i>KCNQ1</i>	27,967	55	119	0.033	-	-	-	-	-	-	-	-
	<i>NGDN</i>	27,967	16	52	0.035	-	-	-	-	-	-	-	-
	<i>WDR48</i>	27,967	15	189	0.047	-	-	-	-	-	-	-	-
	<i>HAND1*</i>	23,567	17	41	2.47E-05	-	-	-	-	11,244	3	4	-
	<i>SCN5A</i>	23,567	176	824	5.70E-04	-	-	-	-	-	-	-	-
PWD	<i>SOX5</i>	23,567	29	46	0.010	-	-	-	-	-	-	-	-
	<i>HES3</i>	23,567	8	445	0.021	-	-	-	-	-	-	-	-
	<i>GORASP1</i>	23,567	24	271	0.030	-	-	-	-	-	-	-	-
	<i>MYH6</i>	23,567	191	794	0.040	-	-	-	-	-	-	-	-
	<i>PAM*</i>	28,008	44	399	4.46E-07	22,436	44	554	0.02	7,136	21	184	0.37
	<i>SCN5A*</i>	28,008	201	1089	7.62E-07	22,436	96	352	0.013	7,136	44	98	1.52E-04
PR	<i>MYH6</i>	28,008	203	900	0.006	-	-	-	-	-	-	-	-
	<i>CMTM5</i>	28,008	10	18	0.006	-	-	-	-	-	-	-	-
	<i>ACOT7</i>	28,008	9	12	0.008	-	-	-	-	-	-	-	-
	<i>HAND1</i>	28,008	17	45	0.015	-	-	-	-	-	-	-	-
	<i>MICU2</i>	28,008	34	330	0.024	-	-	-	-	-	-	-	-
	<i>NKX2-5</i>	28,008	22	78	0.026	-	-	-	-	-	-	-	-
	<i>OLFM1.2B</i>	28,008	57	275	0.031	-	-	-	-	-	-	-	-
	<i>NR3C2</i>	28,008	41	68	0.039	-	-	-	-	-	-	-	-
	<i>KCNH2</i>	28,008	66	330	0.039	-	-	-	-	-	-	-	-
	<i>TMEM182</i>	28,008	17	41	0.042	-	-	-	-	-	-	-	-
	<i>CR1L*</i>	27,874	18	143	1.22E-04	-	-	-	11,356	8	16	0.91	-
	<i>ZDHHC20</i>	27,874	11	19	0.001	-	-	-	-	-	-	-	-
	<i>CHD5</i>	27,874	94	215	0.017	-	-	-	-	-	-	-	-
	<i>GPR153</i>	27,874	17	27	0.020	-	-	-	-	-	-	-	-
QRS	<i>SCN5A</i>	27,874	199	1084	0.026	-	-	-	-	-	-	-	-
	<i>KIAA1755</i>	27,874	32	215	0.026	-	-	-	-	-	-	-	-
	<i>RNF207</i>	27,874	24	33	0.037	-	-	-	-	-	-	-	-
	<i>LITAF</i>	27,874	20	50	0.042	-	-	-	-	-	-	-	-
	<i>MEGE8</i>	27,874	61	518	0.050	-	-	-	-	-	-	-	-
	<i>KCNQ1*</i>	26,976	55	115	2.31E-12	20,366	24	56	1.10E-10	7,013	11	22	0.039
	<i>KCNH2*</i>	26,976	63	319	3.18E-08	20,366	29	60	0.049	7,013	10	13	0.35
	<i>SKI</i>	26,976	38	126	0.004	-	-	-	-	-	-	-	-
QTc	<i>SH3PXD2A</i>	26,976	16	43	0.02	-	-	-	-	-	-	-	-
	<i>LITAF</i>	26,976	20	49	0.025	-	-	-	-	-	-	-	-
	<i>RNF207</i>	26,976	24	32	0.030	-	-	-	-	-	-	-	-
	<i>TBX3</i>	26,976	43	83	0.039	-	-	-	-	-	-	-	-
	<i>OLFM1.2B</i>	26,976	55	263	0.041	-	-	-	-	-	-	-	-
	<i>SYNPOL2L</i>	26,976	16	28	0.04	-	-	-	-	-	-	-	-
	<i>HCN1</i>	26,976	14	22	0.049	-	-	-	-	-	-	-	-

Note: All gene-trait associations reaching at least nominal significance ($P < 0.05$) are shown here. * indicates that a gene-trait association reached analysis-wide bonferroni-corrected significance. ECG, electrocardiogram; cMAC, cumulative minor allele count; PWD, P-wave duration; QTc, Bazett-corrected QT interval; meta, meta-analysis.

Supplemental Table VII. Results from collapsed tests of LOF and likely pathogenic variants in TOPMed, UK Biobank and MyCode including overall meta-analysis

Individual cohorts											TOPMed					3-lead UK Biobank				
Trait	Groups	Gene(s)	N carriers	N controls	βeta	95% CI	P value	N carriers	N	N controls	βeta	95% CI	P value							
PR	LOF	PAM	14	27994	-18.24	[-31.79, -4.68]	8.38E-03	10	22426	-7.83	[-21.81, 6.15]	0.27								
	Pathogenic	SCN5A	9	27999	20.88	[3.73, 38.03]	0.017	10	22426	20.52	[6.54, 34.5]	4.00E-03								
LOF	LOF	KCNQ1	21	27987	18.0	[7.39, 28.65]	8.93E-04	12	22424	11.8	[-0.96, 24.57]	0.07								
	Pathogenic	SCN5A	16	26960	33.98	[23.04, 44.91]	1.11E-09	9	20357	56.16	[41.16, 71.16]	2.13E-13								
LOF	LOF	KCNH2	5	26971	59.17	[39.6, 78.74]	3.10E-09	4	20362	4.88	[-17.61, 27.36]	0.67								
	Pathogenic	SCN5A	9	26967	5.5	[-10.04, 20.98]	0.49	8	20358	14.0	[-1.87, 29.92]	0.08								
LOF	LOF	KCNQ1, KCNH2	21	26955	40.0	[30.44, 49.52]	2.13E-16	13	20353	40.4	[27.9, 52.85]	2.25E-10								
	Pathogenic	KCNQ1, SCN5A	30	26946	30.5	[22.37, 38.62]	1.90E-13	21	20345	30.3	[20.52, 40.15]	1.38E-09								
Pathogenic	Pathogenic	KCNQ1	52	26924	28.3	[22.76, 33.8]	1.00E-23	21	20345	33.8	[24, 43.63]	1.44E-11								
	Pathogenic	KCNH2	11	26965	33.3	[20.57, 46.1]	3.06E-07	10	20356	23.0	[8.76, 37.21]	1.54E-03								
Pathogenic	Pathogenic	SCN5A	19	26957	1.9	[-8.21, 12.07]	0.71	10	20356	-0.2	[-14.43, 14.01]	0.98								
	Pathogenic	KCNQ1, KCNH2	63	26913	29.1	[24.02, 34.15]	2.10E-29	31	20335	30.3	[22.26, 38.42]	1.85E-13								
Pathogenic	Pathogenic	KCNQ1, KCNH2, SCN5A	82	26894	23.7	[19.12, 28.18]	1.41E-24	41	20325	22.9	[15.87, 29.93]	1.70E-10								
	Pathogenic	LQT5 gene panel *	142	26834	15.1	[11.52, 18.63]	8.64E-17	68	20298	18.0	[12.53, 23.45]	1.08E-10								
Pathogenic	LOF + Pathogenic	KCNQ1	55	26921	28.2	[22.77, 33.59]	1.95E-24	22	20344	34.1	[24.54, 43.72]	3.03E-12								
	Pathogenic	KCNH2	12	26964	31.4	[19.24, 43.61]	4.33E-07	13	20353	15.8	[3.37, 28.33]	0.01								
Pathogenic	LOF + Pathogenic	SCN5A	26	26950	3.1	[5.71, 11.93]	0.49	12	20354	3.4	[-9.63, 16.33]	0.61								
	Pathogenic	KCNQ1, KCNH2	67	26909	28.7	[23.78, 33.67]	4.96E-30	35	20331	27.4	[19.75, 34.97]	1.78E-12								
Pathogenic	LOF + Pathogenic	KCNQ1, KCNH2, SCN5A	93	26883	22.6	[18.27, 26.9]	1.04E-24	47	20319	21.2	[14.68, 27.8]	2.27E-10								
12-lead UK Biobank																				
PR	LOF	PAM	5	7131	-12.96	[-35.18, 9.26]	0.25	23	84560	7.51	[-3.86, 18.88]	0.2								
	Pathogenic	SCN5A	8	7128	25.75	[8.19, 43.31]	4.04E-03	43	84540	50.94	[42.71, 59.17]	2.90E-33								
LOF	LOF	KCNQ1	2	7008	28.1	[-5.49, 61.69]	0.06	73	84510	44.0	[37.62, 50.36]	1.20E-41								
	Pathogenic	KCNH2	2	7005	11.28	[-22.31, 44.88]	0.51	10	88256	50.7	[31.88, 69.52]	1.20E-07								
LOF	LOF	SCN5A	7	7006	-9.9	[-27.85, 8.13]	0.28	40	88226	-2.1	[-11.51, 7.31]	0.66								
	Pathogenic	KCNQ1, KCNH2	4	7009	19.6	[-4.16, 43.39]	0.11	61	88205	44.6	[37.0, 52.2]	1.60E-30								

	LOF	KCNQ1, KCNH2, SCN5A	11	7002	0.9	[-13.48, 15.22]	0.91	101	88165	26.1	[20.2, 32.0]	5.00E-18
Pathogenic	KCNQ1	5	7008	26.5	[5.2, 47.73]	0.01	133	88133	31.4	[26.28, 36.58]	6.90E-33	
Pathogenic	KCNH2	1	7012	12.3	[-35.26, 59.86]	0.61	33	88233	29.0	[18.65, 39.35]	3.90E-08	
Pathogenic	SCN5A	11	7002	-9.3	[-23.65, 5.05]	0.20	71	88195	7.1	[0.04, 14.16]	0.048	
Pathogenic	KCNQ1, KCNH2	6	7007	24.1	[4.7, 43.54]	0.01	166	88100	30.96	[26.33, 35.59]	1.80E-39	
Pathogenic	KCNQ1, KCNH2, SCN5A	17	6996	2.5	[-9.04, 14.06]	0.67	237	88029	23.8	[19.98, 27.70]	1.20E-33	
Pathogenic	LQTS gene panel*	28	6985	-1.1	[-10.14, 7.87]	0.81	-	-	-	-	-	
Pathogenic	LOF + Pathogenic	KCNQ1	5	7008	26.5	[5.2, 47.73]	0.01	142	88124	30.66	[25.66, 35.66]	2.20E-33
Pathogenic	LOF + Pathogenic	KCNH2	3	7010	11.6	[15.85, 39.04]	0.41	39	88227	31.59	[22.06, 41.12]	7.70E-11
Pathogenic	LOF + Pathogenic	SCN5A	11	7002	-9.3	[-23.65, 5.05]	0.20	87	88179	5.2	[-1.14, 11.60]	0.11
Pathogenic	LOF + Pathogenic	KCNQ1, KCNH2	8	7005	20.9	[4.09, 37.72]	0.01	181	88085	30.88	[26.45, 35.31]	1.20E-42
Pathogenic	LOF + Pathogenic	KCNQ1, KCNH2, SCN5A	19	6994	3.4	[7.49, 14.36]	0.54	268	87998	22.58	[18.95, 26.21]	4.40E-34
<i>Meta-analysis results</i>												
TOPMed + UK Biobank												
inverse-variance fixed effects												
random effects (Paule-Mandel**)												
	N carriers	N controls	beta	95% CI	P value	beta	95% CI	P value				
PR	LOF	<i>PAM'</i>	29	57551	-13.15	[-22.06, -4.24]	3.80E-03	-13.2	[-22.06, -4.24]	3.80E-03		
	LOF	SCN5A	27	57553	22.07	[12.86, 31.28]	2.65E-06	22.1	[12.86, 31.28]	2.65E-06		
PTC	Pathogenic	SCN5A	44	57536	15.25	[8.07, 22.42]	3.09E-05	15.2	[8.07, 22.42]	3.09E-05		
	LOF	KCNQ1	27	54325	40.79	[32.25, 49.33]	8.15E-21	41.5	[25.18, 57.76]	6.08E-07		
	LOF	KCNH2	11	54338	31.80	[18.29, 45.32]	3.98E-06	26.3	[-8.06, 60.64]	1.34E-01		
	LOF	SCN5A	24	54331	4.26	[-5.18, 13.71]	3.76E-01	3.8	[-9.64, 17.18]	5.82E-01		
	LOF	KCNQ1, KCNH2	38	54317	38.23	[31.01, 45.45]	3.08E-25	37.1	[26.91, 47.23]	8.54E-13		
	LOF	KCNQ1, KCNH2, SCN5A	62	54293	25.71	[19.97, 31.14]	1.60E-18	21.3	[2.39, 40.21]	2.73E-02		
	Pathogenic	KCNQ1	78	54277	29.46	[24.76, 34.15]	8.61E-35	29.5	[24.76, 34.15]	8.61E-35		
	Pathogenic	KCNH2	22	54333	28.09	[18.78, 37.41]	3.41E-09	28.1	[18.78, 37.41]	3.41E-09		
	Pathogenic	SCN5A	40	54315	-1.40	[-8.56, 5.75]	7.01E-01	-1.4	[-8.56, 5.75]	7.01E-01		
	Pathogenic	KCNQ1, KCNH2	100	54255	29.19	[25, 33.38]	1.84E-42	29.2	[25, 33.38]	1.84E-42		
	Pathogenic	KCNQ1, KCNH2, SCN5A	140	54215	21.38	[17.76, 25]	4.73E-31	17.2	[4.06, 30.31]	1.03E-02		
	Pathogenic	LQTS gene panel*	238	54117	14.26	[11.43, 17.08]	4.68E-23	11.2	[-0.13, 22.53]	5.27E-02		
	LOF + Pathogenic	KCNQ1	82	54273	29.47	[24.87, 34.07]	3.99E-36	29.5	[24.87, 34.07]	3.99E-36		

PR	Pathogenic	LOF + Pathogenic	KCNH2	28	54327	22.70	[14.39, 31.01]	8.59E-08	21.9	[10.33, 33.55]	2.12E-04
	Pathogenic	LOF + Pathogenic	SCN5A	49	54306	0.62	[5.88, 7.13]	8.51E-01	0.4	[6.87, 7.62]	9.20E-01
	Pathogenic	LOF + Pathogenic	KCNQ1, KCNH2	110	54245	27.89	[23.87, 31.92]	5.08E-42	27.9	[23.87, 31.92]	5.08E-42
	Pathogenic	LOF + Pathogenic	KCNQ1, KCNH2, SCN5A	159	54196	20.34	[16.92, 23.76]	2.44E-31	16.6	[4.96, 28.24]	5.20E-03
											TOPMed + UK Biobank + MyCode
	LOF	PAM'	PAM'	52	142111	-5.3	[-12.3, 1.72]	1.39E-01	-6.8	[-18.36, 4.68]	0.2445
	LOF	SCN5A	SCN5A	70	142093	38.1	[31.98, 44.26]	4.33E-34	30.3	[12.23, 48.44]	0.001
	Pathogenic	SCN5A	SCN5A	117	142046	31.3	[26.55, 36.08]	5.33E-38	22.7	[4.57, 40.74]	0.014
	LOF	KCNQ1	KCNQ1	78	142540	42.2	[36.22, 48.08]	3.88E-44	42.3	[31.91, 52.67]	1.411E-15
	LOF	KCNH2	KCNH2	21	142594	38.2	[27.27, 49.21]	8.53E-12	33.0	[6.02, 60.02]	0.017
	LOF	SCN5A	SCN5A	64	142557	1.1	[-5.60, 7.74]	7.50E-01	1.7	[-7.53, 10.88]	0.72
	LOF	KCNQ1, KCNH2	KCNQ1, KCNH2	99	142522	41.3	[36.03, 46.50]	7.48E-54	40.1	[32.65, 47.56]	5.45E-26
	LOF	KCNH2, SCN5A	KCNH2, SCN5A	163	142458	25.9	[21.78; 30.01]	5.53E-35	23.5	[13.99; 33.07]	1.338E-06
	Pathogenic	KCNQ1	KCNQ1	211	142410	30.4	[26.88, 33.82]	7.03E-66	30.4	[26.88, 33.82]	7.034E-66
	Pathogenic	KCNH2	KCNH2	55	142566	28.5	[21.57, 35.42]	7.18E-16	28.5	[21.57, 35.42]	7.181E-16
	Pathogenic	SCN5A	SCN5A	111	142510	2.9	[-2.12, 7.93]	2.60E-01	1.9	[-4.47, 8.3]	0.56
	Pathogenic	KCNQ1, KCNH2	KCNQ1, KCNH2	266	142355	29.9	[27.04, 32.79]	1.90E-92	29.9	[27.04, 32.79]	1.899E-92
	Pathogenic	KCNQ1, KCNH2, SCN5A	KCNQ1, KCNH2, SCN5A	377	142244	23.8	[21.30, 26.31]	2.83E-77	21.67 **	[15.36, 27.98] **	1.7E-11 **
	LOF + Pathogenic	KCNQ1	KCNQ1	224	142397	30.0	[26.64, 33.41]	1.06E-67	30.0	[26.64, 33.41]	1.063E-67
	LOF + Pathogenic	KCNH2	KCNH2	67	142554	26.5	[20.26, 32.79]	1.03E-16	25.3	[16.05, 34.55]	8.245E-08
	Pathogenic	LOF + SCN5A	SCN5A	136	142485	3.0	[-1.58, 7.52]	2.00E-01	2.7	[-2.31, 7.73]	0.29
	Pathogenic	LOF + KCNQ1, KCNH2	KCNQ1, KCNH2	291	142330	29.2	[26.27, 32.22]	1.73E-82	29.2	[26.27, 32.22]	1.726E-82
	Pathogenic	LOF + SCN5A	SCN5A	427	142194	21.4	[18.91, 23.88]	1.12E-63	18.5	[10.01, 26.93]	1.88E-05

Note: LOF, loss-of-function; Pathogenic: likely pathogenic and pathogenic variants, CI, confidence interval; QTc, Bazett-corrected QT interval * for QTc analysis only data for canonical LQTS genes was produced

Supplemental Table VIII. Clinical characteristics of LOF variant carriers for PAM, SCN5A, KCNQ1 and KCNH2 in TOPMed, UK Biobank and MyCode

Gene	Subj	Lead	Variant_id	cDNA.c	Protein.c	Csq	Combined_c*	HR	PR	PWD	QRS	QTc	Age	Sex	Anc	BB	CCB	MI	HF
TOPMed																			
	1		5:1029139 48:C>T	c.283C>T	p.Arg95Ter	stop_gained	-	80	130	100	100	465	75	F	EUR	0	1	0	0
	2		5:1029265 84:G>A	c.443-1G>A	.	splice_acce prior_variant	-	52	144	96	86	422	45	F	EUR	0	0	0	0
	3		5:1029265 84:G>A	c.443-1G>A	.	splice_acce prior_variant	-	83	146	108	90	441	65.1	M	EUR	0	0	0	0
	4		5:1029468 41:T>AA	c.532_533dup AA	p.Asn178 LysfsTer1	frameshift_V ariant	-	55	116	106	84	436	59	F	AFR	0	0	1	0
	5		5:1029468 41:T>AA	c.532_533dup AA	p.Asn178 LysfsTer1	frameshift_V ariant	-	44	156	96	88	379	58.7	F	AFR	0	0	0	0
	6		5:1029495 47:T>T	c.655delG	p.Asp219 ThrsTer2	frameshift_V ariant	-	56	172	114	96	389	53	M	EUR	0	0	0	0
	7		5:1029499 46:CTGAT: C	c.772_775del ATTG	p.Ile258A stopTer20	frameshift_V ariant	-	85	156	104	82	454	65	F	EUR	0	0	0	0
	8		5:1029612 14:GAA GT: G	c.1148_1151d elAA GT	p.Glu383 GlyfsTer2	frameshift_V ariant	-	67	156	142	76	407	64	F	EUR	0	0	0	0
	9		5:1029902 99:G>A	c.1511G>A	p.Trp04 Ter	stop_gained	-	64	142	120	100	454.4	74	F	UND	0	0	0	0
	10		5:1030173 32:A>T	c.2332-2A>T	.	splice_acce prior_variant	-	63	120	98	108	423	48.1	M	EUR	0	0	0	0
	11	lead	5:1030173 32:A>T	c.2332-2A>T	.	splice_acce prior_variant	-	51	140	114	102	407	44.3	M	EUR	0	0	0	0
	12		5:1030173 32:A>T	c.2332-2A>T	.	splice_acce prior_variant	-	52	146	126	98	416	71.0	F	EUR	1	0	0	0
	13		5:1030173 32:A>T	c.2332-2A>T	.	splice_acce prior_variant	-	61	152	112	104	442	40	M	EUR	0	0	0	0
	14		5:1030173 32:A>T	c.2332-2A>T	.	splice_acce prior_variant	-	69	176	106	92	439	67.6	M	EUR	0	0	0	0
	1		3:3856241 3:3856243	c.3963+2T>C	.	splice_donor _variant	-	60	186	128	90	410	83.3	F	EUR	0	0	0	0
	2		3:3856243 2:G>A	c.3946C>T	p.Arg131 6Ter	stop_gained	-	42	250	132	120	428.4	69	M	EUR	0	0	0	0
	3		3:3857539 0:C>T	c.3573G>A	p.Trp1191 Ter	stop_gained	-	58	190	134	108	418	47	M	EUR	0	0	0	0
	4		3:3858094 5:C>A	c.3214G>T	p.Glu107 2Ter	stop_gained	-	68	144	112	88	456	43.2	F	AFR	0	0	0	0
	5		3:3858094 5:C>A	c.3214G>T	p.Glu107 2Ter	stop_gained	-	65	146	100	104	437	36.6	F	AFR	0	0	0	0
	6		3:3858094 5:C>A	c.3214G>T	p.Glu107 2Ter	stop_gained	-	61	152	114	110	405	47	M	AFR	0	0	0	0
	7		3:3859900 4:TG>T	c.3244G>T	p.Glu107 2Ter	stop_gained	-	53	162	126	96	457	62.1	F	AFR	0	0	0	0
	8		3:3859900 4:TG>T	c.1936delC	p.Gln646 ArgfsTer5	frameshift_V ariant	-	59	204	112	100	409	53	F	AFR	0	0	0	0
	9		3:3880815 0:C>A	c.998+1G>T	.	splice_donor _variant	-	55	242	-	104	438	62.9	M	AFR	1	0	-	-

1	11:244520 0:C:A	c.102C>A	p.Cys34T er	stop_gained	-	65	120	176	92	460	43.0	F	AFR	0	0	0	0
2	11:244525 1:C:G	c.153C>G	p.Ty51Te r	stop_gained	-	70	114	182	92	436	49.7	M	EUR	0	0	0	0
3	11:244525 1:C:G	c.153C>G	p.Ty51Te r	stop_gained	-	63	136	190	100	464	79.2	M	EUR	0	1	0	0
4	11:244529 4:TC:T	c.200deIC	p.Pro67Ar gfsTer9	frameshift_v ariant	-	73	96	132	86	458	54.0	F	AFR	0	0	0	0
5	11:257071 9:GGCTG C:G	c.573_577del	CysfsTer9 1	frameshift_v ariant	-	61	132	170	82	424	73.0	F	EUR	0	0	0	0
6	11:257071 C:G	c.573_577del	p.Arg192 CysfsTer9	frameshift_v ariant	-	66	98	188	90	480	51.0	F	EUR	0	0	0	0
7	11:257285 8:AC:A	c.796delC	p.Leu266 CysfsTer2 3	frameshift_v ariant	-	58	104	156	68	453	64.0	F	EUR	0	0	0	0
8	11:257285 8:AC:A	c.796delC	p.Leu266 CysfsTer2 3	frameshift_v ariant	-	60	108	160	90	488	64.0	F	EUR	0	0	0	0
9	11:257297 3:T:TG	c.909dupG	p.Trp304 ValfsTer1 59	frameshift_v ariant	-	57	112	198	108	432	46.0	M	UND	0	0	0	0
10	11:258354 6:G:A	c.1032+1G>A	-	splice_donor variant	-	89	-	-	82	515	79.0	M	EUR	1	0	1	1
11	11:258763 6:G:GC	c.1201dupC	p.Arg401 ProfsTer6 2	frameshift_v ariant	-	54	102	156	86	419	45.3	M	EUR	0	0	0	0
12	11:258763 6:G:GC	c.1201dupC	p.Arg401 ProfsTer6 2	frameshift_v ariant	-	71	118	164	106	449	68.3	M	EUR	0	1	0	0
13	11:258885 5:G:A	c.1393+1G>A	-	splice_donor variant	-	57	-	160	90	449	65.8	M	SAS	1	0	-	-
14	11:276888 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	55	120	162	86	494	63.3	F	UND	0	0	0	0
15	11:276891 7:C:T	c.1588C>T	p.Gln530	stop_gained, splice_region	-	55	112	198	92	445	55.0	M	EUR	0	0	0	0
16	11:277698 4:A:G	c.1686-2A>G	-	splice_acce n_variant	-	64	-	182	90	427	49.8	M	SAS	1	1	1	-
1	7:1509473 C:T	c.3099_3109d	p.Pro103 CGGGGG GCCG	frameshift_v ariant	-	57	98	150	84	434	53.0	F	EUR	0	0	0	0
2	7:1509474 40:G:A	c.3040C>T	p.Arg101 4Ter	stop_gained	-	54	118	180	106	442	45.1	M	AFR	0	0	0	0
3	7:1509478 42:G:GGC CCC	c.272_2728d	p.Pro910 ArgfsTer6 6	frameshift_v ariant	-	77	116	170	86	531	63.7	M	EUR	0	0	0	0
4	7:1509478 42:G:GGC CCC	c.272_2728d	p.Pro910 ArgfsTer6 6	frameshift_v ariant	-	52	100	174	78	478	63.5	F	EUR	0	0	0	0
5	7:1509478 42:G:GGC CCC	c.272_2728d	p.Pro910 ArgfsTer6 6	frameshift_v ariant	-	42	102	188	110	504	37.0	M	EUR	0	0	0	0
UK Biobank																	
PAM	1 2	3-lead 5:1030198 42:AG:A 5:1030198 42:AG:A	c.2485+1del c.2485+1del c.2485+1del c.2485+1del	- frameshift_v ariant ariant	- frameshift_v ariant ariant	- 66 93	114 132	70 76	453 406	86 86	59 44	F M	EUR EUR	0 0	0 0	0 0	0 0

3	5:1029495 47:T;T	c.655del	p.Asp219 T <hr/> Ter2 3	frameshift_v ariant	-	64	136	84	407	70	57	F	EUR	0	0	0	0
4	5:1029495 47:T;T	c.655del	p.Asp219 T <hr/> Ter2 3	frameshift_v ariant	-	65	134	142	420	88	51	M	EUR	0	0	0	0
5	5:1029742 06:C;G	c.1253C>G	p.Ser418 Ter	stop_gained	-	81	146	74	448	104	51	F	EUR	0	0	0	0
6	5:1029744 37:G;T	c.1253C>G	p.Ser418 Ter	stop_gained	-	75	112	76	373	72	59	M	EUR	0	0	0	0
7	5:103075 85:AC;A	c.1483+1G>T	-	splice_donor variant	-	74	124	104	424	68	54	F	EUR	0	0	0	0
8	5:1030198 44:G;C	c.2145del	p.Glu717 AsnfsTer3	frameshift_v ariant	-	80	152	78	406	74	43	F	EUR	0	0	0	0
9	5:1030251 29:A;G	c.2485+1G>C	-	splice_donor variant	-	68	146	100	383	96	46	M	EUR	0	1	0	0
10	5:1028662 04:CCG;C	c.12_13del	p.Val5Pro fsTer2	frameshift_v ariant	-	62	152	102	397	92	54	F	EUR	0	0	0	0
11	5:1029499 46:CTGAT; C	c.772_775del	p.Ile258A SpfsTer20	frameshift_v ariant	-	77	140	78	461	98	76	F	EUR	0	0	0	0
12	5:1030289 42:C;G	c.2802C>G	p.Tyr93T er	stop_gained	-	70	156	104	447	86	74	M	EUR	0	0	0	0
13	5:1029495 47:1G;T	c.655del	p.Asp219 Ter	frameshift_v ariant	-	58	144	98	406	100	57	M	EUR	0	0	0	0
14	5:1029174 14:G;A	c.2412G>A	p.Trp804 Ter	stop_gained	-	61	148	78	432	84	55	F	EUR	0	0	0	0
15	3:3855050 0:G;A	c.5872C>T	p.Arg195 8Ter	stop_gained	-	74	138	90	378	90	54	M	EUR	0	0	0	0
1	3:3855054 5:CA;G;C	c.5825_5826d el	p.Pro194 2ArgfsTer 12	frameshift_v ariant	-	58	192	90	417	90	47	M	EUR	0	0	0	0
2	3:3855054 5:CA;G;C	c.5825_5826d el	p.Pro194 2ArgfsTer 12	frameshift_v ariant	-	65	150	100	425	86	49	F	EUR	0	0	0	0
3	3:3855054 5:CA;G;C	c.5825_5826d el	p.Pro194 2ArgfsTer 12	frameshift_v ariant	-	77	98	292	458	78	57	F	EUR	0	0	0	0
4	3:3855054 5:CA;G;C	c.5825_5826d el	p.Pro194 2ArgfsTer 12	frameshift_v ariant	-	77	98	292	458	78	57	F	EUR	0	0	0	0
5	3:3855150 5:G;A	c.4867C>T	p.Arg162 Ter	stop_gained	-	52	170	104	408	116	50	F	EUR	0	0	0	0
6	3:3859788 3:C-T	c.2108G>A	p.Trp703 Ter	stop_gained	-	62	226	114	488	112	52	F	EUR	0	0	0	0
8	3:3860399 9:G;A	c.1603C>T	p.Arg335 Ter	stop_gained	-	80	180	124	427	138	59	M	EUR	1	0	0	0
9	3:3861406 3:A;C	c.615T>G	p.Tyr205T er	stop_gained	-	73	152	94	470	92	52	F	EUR	0	0	0	0
10	3:3861406 3:A;C	c.615T>G	p.Tyr205T er	stop_gained	-	51	178	84	389	68	57	M	EUR	0	0	0	0
11	3:3861406 3:A;C	c.615T>G	p.Tyr205T er	stop_gained	-	71	180	82	435	94	47	F	EUR	0	0	0	0
12	3:3861406 3:A;C	c.615T>G	p.Tyr205T er	stop_gained	-	60	174	94	420	92	52	F	EUR	0	0	0	0
13	12:lead	c.615T>G	p.Tyr205T er	stop_gained	-	67	148	74	399	98	66	F	EUR	0	0	0	0
14	3:3861406 3:A;C	c.615T>G	p.Tyr205T er	stop_gained	-	68	168	82	435	96	68	F	EUR	0	0	0	0

SCN5A

15	3:3861406 3:A:C	c.615T>G p.Tyr205T er	p.Tyr205T stop_gained	-	60	132	82	412	94	74	F	EUR	0	0	0	0	
16	3:A:C	c.615T>G p.Tyr205T er	p.Tyr205T stop_gained	-	60	214	98	394	120	59	F	EUR	0	0	0	0	
17	3:3861406 3:A:C	c.615T>G p.Tyr205T er	p.Tyr205T stop_gained	-	62	158	88	426	92	65	M	EUR	0	0	0	0	
18	3:3866640 8:C:T	c.3840+1G>A -	splice_donor variant	-	63	238	90	403	98	71	M	EUR	0	0	0	0	
19	3:3862087 0:CA:C	c.583del p.Trp195 GlyfsTer6	p.Trp195 frameshift_v GlyfsTer6	ariant	-	64	274	130	412	90	63	M	EUR	0	0	0	0
16	3:3861406 3:A:C	c.615T>G p.Tyr205T er	p.Tyr205T stop_gained	-	60	214	98	394	120	59	F	EUR	0	0	0	0	
17	3:3861406 3:A:C	c.615T>G p.Tyr205T er	p.Tyr205T stop_gained	-	62	158	88	426	92	65	M	EUR	0	0	0	0	
18	3:3866640 8:C:T	c.3840+1G>A -	splice_donor variant	-	63	238	90	403	98	71	M	EUR	0	0	0	0	
19	3:3862087 0:CA:C	c.583del p.Trp195 GlyfsTer6	p.Trp195 frameshift_v GlyfsTer6	ariant	-	64	274	130	412	90	63	M	EUR	0	0	0	0
1	11:257063 7:CTC	c.488del ArgfTer7	p.Leu163 ArgfTer7	frameshift_v ariant	-	64	146	72	454	120	54	F	EUR	1	0	0	0
2	11:257066 4:GGGTC CGCCCTC: G	c.524_534del CysfTer1	p.Leu175 CysfTer1	frameshift_v ariant	-	62	152	70	437	88	59	F	EUR	0	0	0	0
3	11:257071 9:GGCTG C:G	c.573_577del CysfTer9	p.Arg192 CysfTer9	frameshift_v ariant	-	71	160	94	490	108	46	F	EUR	0	0	0	0
4	11:257071 9:GGCTG C:G	c.573_577del CysfTer9	p.Arg192 CysfTer9	frameshift_v ariant	-	75	130	88	472	98	50	M	EUR	0	0	0	0
5	11:257071 8:TGG:T	c.918_919del GlyfsTer1	p.Val307 GlyfsTer1	frameshift_v ariant	-	65	166	86	456	94	50	F	EUR	0	0	0	0
6	11:258351 9:GC:G	c.1008del GlyfsTer17	p.Ile337S GlyfsTer17	frameshift_v ariant	-	58	184	100	519	94	52	F	EUR	0	0	0	0
7	11:266196 0:G:T	c.1394_1G>T -	splice_acce prior_variant	-	59	154	88	500	122	57	F	EUR	0	0	0	0	
8	11:266196 0:G:T	c.1394_1G>T -	splice_acce prior_variant	-	83	152	78	475	92	56	F	EUR	0	0	0	0	
9	11:266196 0:G:T	c.1394_1G>T -	splice_acce prior_variant	-	84	136	90	424	76	58	M	EUR	0	0	0	0	
10	11:266196 0:G:T	c.1394_1G>T -	splice_acce prior_variant	-	59	130	94	455	98	60	M	EUR	0	0	0	0	
11	11:257071 9:GGCTG	c.573_577del CysfTer9	p.Arg192 CysfTer9	frameshift_v ariant	-	63	176	88	435	108	68	F	EUR	0	0	0	0
1	7:1509477 9:GC:G	c.2775del ArgfTer4	p.Pro926 ArgfTer4	frameshift_v ariant	-	81	110	90	451	82	50	M	EUR	0	0	0	0
2	7:1509501 7:2:GAT:G	c.2392_2393d el	p.Ile798Pr ofTer5	frameshift_v ariant	-	66	150	72	409	116	60	M	EUR	0	0	0	0
3	7:1509501 7:2:GAT:G	c.2392_2393d el	p.Ile798Pr ofTer5	frameshift_v ariant	-	69	160	86	408	100	61	F	EUR	0	0	0	0

KCNQ1

7:1509573 62:TGGGC ;T & 7:1509573 69:AGCCA GAAAGG GTC:A	c.1053_1056d el & c.1036_1049d el	p.Th353 ValfsTer6 & p.Asp346 PhefsTer 5	frame shift_v frame shift_v frame shift_v frame shift_v	in frame deletion	68	128	92	398	94	60	M	EUR	0	0	0	0	0	0	0	
5 6	12- lead	7:1509778 96:GC:G	c.2090_2091i nsC	p.Lys897 AsnfsTer2 3	frame shift_v frame shift_v frame shift_v	-	66	164	114	413	112	65	M	EUR	0	0	0	0	0	
1	5:1029495 47:TG:T	c.655del	p.Asp219 ThrfsTer2 3	frame shift_v frame shift_v	-	69	174	98	458	96	65	M	-	0	0	0	0	0	0	
2	5:1029003 93:G:A	c.1605G>A	p.Trp535 Ter	stop_gained	-	69	124	84	417	88	51	F	-	0	0	0	0	0	0	
3	5:1029495 47:TG:T	c.655del	p.Asp219 ThrfsTer2 3	frame shift_v frame shift_v	-	78	148	94	426	92	19	F	-	0	0	0	0	0	0	
4	5:1029499 00:A:C	c.725-2A>C	-	splice_acce ptor_variant	-	84	152	92	472	106	72	F	-	0	0	1	0	0	0	
5	5:102942 44:CA:C	c.1298del	p.Lys433 ArgfsTer3 2	frame shift_v frame shift_v	-	74	164	110	463	126	82	M	-	0	0	0	0	0	0	
6	5:1029495 47:TG:T	c.655del	p.Asp219 ThrfsTer2 3	frame shift_v frame shift_v	-	78	142	92	437	106	40	M	-	0	0	0	0	0	0	
7	5:1029903 25:C:T	c.1537C>T	p.Gln513 Ter	stop_gained	-	85	152	86	402	108	48	M	-	0	0	0	0	0	0	
8	5:1029903 93:G:A	c.1605G>A	p.Trp535 Ter	stop_gained	-	84	164	94	457	116	59	M	-	0	0	0	0	0	0	
9	5:1029903 25:C:T	c.1537C>T	p.Gln513 Ter	stop_gained	-	98	174	92	409	118	44	F	-	0	0	0	0	0	0	
10	5:1029903 93:G:A	c.1605G>A	p.Trp535 Ter	stop_gained	-	72	184	110	413	128	49	M	-	0	0	0	0	0	0	
11	5:1029742 44:CA:C	c.1298del	p.Lys433 ArgfsTer3 2	frame shift_v frame shift_v	-	63	186	88	421	120	70	F	-	1	0	0	0	0	0	
12	5:1030076 50:T:A	c.2208T>A	p.Tyr736T Ter	stop_gained	-	75	198	96	442	138	36	F	-	1	0	0	0	0	0	
13	5:1030076 50:T:A	c.2208T>A	p.Tyr736T Ter	stop_gained	-	67	214	102	435	114	65	F	-	1	0	0	1	0	0	
14	5:1029903 93:G:A	c.1605G>A	p.Trp535 Ter	stop_gained	-	79	158	80	472	114	49	F	-	0	0	0	0	0	0	
15	5:1029903 25:C:T	c.1537C>T	p.Gln513 Ter	stop_gained	-	61	220	90	390	118	75	F	-	0	0	0	1	0	0	
16	5:1029741 23:CT:C	c.1171del	p.Tyr391I	frame shift_v	-	66	140	84	434	90	65	F	-	0	0	0	0	0	0	
17	5:1029742 44:CA:C	c.1298del	p.Lys433 ArgfsTer3 2	frame shift_v frame shift_v	-	93	136	78	465	100	49	F	-	0	0	0	0	0	0	
18	5:1029499 00:A:C	c.725-2A>C	-	splice_acce ptor_variant	-	65	170	96	418	108	69	F	-	0	0	0	0	0	0	
19	5:10290251 29:A:G	c.2486-2A>G	-	splice_acce ptor_variant	-	80	192	84	422	118	68	F	-	0	0	0	0	0	0	
20	5:1029507 30:T:G	c.819dup	p.His274 AlafsTer4	frame shift_v frame shift_v	-	74	192	94	428	116	56	M	-	1	1	0	0	0	0	

21	5:1030031 51:T;C	c.1730+2T>C	-	splice_donor variant	-	90	166	92	469	122	69	M	-	0	1	0	0	0
22	5:1028662 59:C;T	c.64C>T	p.Arg22T er	stop_gained	-	97	146	74	472	98	72	F	-	1	0	0	0	1
23	5:1029499 00:A;C	c.725-2A>C	-	splice_acce prior_variant	-	97	142	84	436	94	33	M	-	0	0	0	0	0
1	3:3859900 4:TG;T	c.1936del	p.Gln646 ArgfsTer5	frameshift_v ariant	-	71	198	116	460	124	39	M	-	0	0	0	0	0
2	3:3860976 4:C;A	c.904G>T	p.Glu302 Ter	stop_gained	-	86	198	112	459	128	39	F	-	0	0	0	0	0
3	3:3861378 2:G;A	c.664C>T	p.Arg222 Ter	stop_gained	-	71	190	104	428	122	70	M	-	0	0	1	0	0
4	3:3860378 5:GC;G	c.1816del	p.Ala606 GlnfsTer1 7	frameshift_v ariant	-	72	196	90	427	120	55	F	-	0	0	0	0	0
5	3:3859900 4:TG;T	c.1936del	p.Gln646 ArgfsTer5	frameshift_v ariant	-	79	170	100	426	104	36	F	-	0	0	0	0	0
6	3:3859900 4:TG;T	c.1936del	p.Gln646 ArgfsTer5	frameshift_v ariant	-	67	214	112	412	112	35	F	-	0	0	0	0	0
7	3:3860996 6:T;C	c.704-2A>G	-	splice_acce prior_variant	-	53	192	112	397	132	51	M	-	0	0	0	0	0
8	3:3862097 2:C;T	c.483-1G>A	-	splice_acce prior_variant	-	53	222	114	388	124	40	F	-	0	0	0	0	0
9	3:3861378 2:G;A	c.664C>T	p.Arg222 Ter	stop_gained	-	91	194	112	472	152	52	F	-	0	0	0	1	0
10	3:3860378 5:GC;G	c.1816del	p.Ala606 GlnfsTer1 7	frameshift_v ariant	-	52	198	100	401	122	66	M	-	0	1	0	0	0
11	3:3860378 5:GC;G	c.1816del	p.Ala606 GlnfsTer1 7	frameshift_v ariant	-	86	216	82	421	156	58	F	-	0	0	0	0	0
12	3:3860996 6:T;C	c.704-2A>G	-	splice_acce prior_variant	-	71	206	98	439	118	50	F	-	0	1	0	0	0
13	3:3862097 2:C;T	c.483-1G>A	-	splice_acce prior_variant	-	58	218	124	378	128	17	M	-	0	0	0	0	0
14	3:3860594 9:A;T	c.1338+2T>A	-	splice_donor _variant	-	88	228	118	428	108	64	M	-	0	0	0	0	0
15	3:3862091 9:G;A	c.535C>T	p.Arg179 Ter	stop_gained	-	70	196	106	432	84	71	M	-	1	1	0	1	0
16	3:3860996 6:T;C	c.704-2A>G	-	splice_acce prior_variant	-	65	178	86	436	78	70	F	-	0	0	0	0	0
17	3:3861378 2:G;A	c.664C>T	p.Arg222 Ter	stop_gained	-	60	174	124	460	104	65	M	-	0	0	0	0	0
18	3:38656243 6:CA;G;C	c.3940_3941d el	p.Leu131 4ValfsTer 4	frameshift_v ariant	-	76	182	104	456	150	40	F	-	0	0	0	0	0
19	3:3862249 0:GA	c.393-1C>T	-	splice_acce prior_variant	-	71	160	98	393	116	45	M	-	0	0	0	0	0
20	3:3867945 8:GGGGC CTCT;G	c.3258_3265d el	p.Glu108 7SerfsTer 16	frameshift_v ariant	-	47	218	136	467	88	73	M	-	0	0	0	0	0
21	3:3860379 7:G;T	c.1805C>A	p.Ser602 Ter	stop_gained	-	71	176	80	441	130	55	M	-	0	0	1	0	0
22	3:3860667 4:G;A	c.1135C>T	p.Gln379 Ter	stop_gained	-	58	160	108	429	138	73	F	-	0	0	0	0	0
23	3:3862097 2:C;T	c.483-1G>A	-	splice_acce prior_variant	-	66	256	132	410	144	68	M	-	1	0	0	0	0
24	3:3860399 9:G;A	c.1603C>T	p.Arg535 Ter	stop_gained	-	85	168	96	490	132	30	F	-	0	0	0	0	0

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25	3:3861378 2:G>A	c.664C>T Ter	p.Arg222 stop_gained	-	84	274	98	427	128	82	M	-	0	1	0	0
26	3:3859777 4:G>T	c.2217C>A Ter	p.Tyr739T stop_gained	-	88	244	138	445	144	73	M	-	0	0	0	0
27	3:3880667 4:G:A	c.1135C>T Ter	p.Gln379 stop_gained	-	52	222	100	372	98	49	F	-	0	0	0	0
28	3:3856640 8:C>T	c.3840+1G>A Ter	- splice_donor variant	-	98	184	92	431	128	35	M	-	0	0	0	0
29	3:3862091 9:G:A	c.535C>T Ter	p.Arg179 stop_gained	-	80	236	120	422	140	59	M	-	0	0	0	0
30	3:3880976 4:C>A	c.904G>T Ter	p.Glu302 stop_gained	-	66	204	94	427	132	60	F	-	0	0	0	0
31	3:3862097 2:C>T	c.483-1G>A Ter	- splice_acce prior_variant	-	71	216	108	430	80	77	M	-	0	0	0	0
32	3:3859900 4:TG>T	c.1936del Ter	p.Gln646 frameshift_V ariant	-	75	170	94	424	108	58	F	-	0	0	0	0
33	3:3880667 4:G>A	c.1135C>T Ter	p.Gln379 stop_gained	-	79	186	100	451	126	45	F	-	0	0	0	0
34	3:3861378 2:G>A	c.664C>T Ter	p.Arg222 stop_gained	-	66	208	104	394	120	51	F	-	1	0	0	0
35	3:3857947 6:G>A,G	c.3247del Ter	p.Ser108 frameshift_V ariant	-	85	186	130	426	144	71	M	-	0	0	0	0
36	3:3858739 8:A>T	c.243G>T>A - Ter	- splice_donor variant	-	72	132	86	405	124	64	M	-	1	0	0	0
37	3:3855441 8:G>GTTG	c.4669_4673d up	p.Asn155 frameshift_V ariant	-	60	194	96	414	112	77	F	-	0	0	0	0
38	3:3862091 9:G>A	c.535C>T Ter	p.Arg179 stop_gained	-	65	178	244	567	0	70	M	-	1	0	0	1
39	3:3861378 2:G>A	c.664C>T Ter	p.Arg222 stop_gained	-	76	246	162	479	130	48	M	-	0	0	0	0
40	3:3858728 6:T>C	c.4246-2A>G - Ter	- splice_acce prior_variant	-	86	188	110	442	136	43	F	-	0	0	0	0
41	3:3860594 9:A>T	c.1338+2T>A - Ter	- splice_donor variant	-	84	194	106	458	126	66	F	-	0	0	0	0
42	3:3859900 4:TG>T	c.1936del Ter	p.Gln646 frameshift_V ariant	-	77	200	116	430	120	31	M	-	0	0	0	0
43	3:3880399 9:G>A	c.1603C>T Ter	p.Arg35 stop_gained	-	85	170	88	426	126	40	F	-	0	0	0	0
1	11:266196 0:G>T	c.1394-1G>T - Ter	- splice_acce prior_variant	-	61	176	106	440	126	46	M	-	0	0	0	0
2	11:257140 4:G>A	c.683+1G>A - Ter	- splice_donor variant	-	61	160	84	420	112	51	M	-	0	0	0	0
3	11:266196 0:G>T	c.1394-1G>T - Ter	- splice_acce prior_variant	-	82	152	74	455	58	53	F	-	0	0	0	0
4	11:257065 1:CG>C	c.502del Ter	p.Thr169 frameshift_V ariant	-	56	172	90	476	94	55	F	-	0	0	0	0
5	11:257140 4:G>A	c.683+1G>A - Ter	- splice_donor variant	-	70	130	86	434	96	49	F	-	0	0	0	0
6	11:258871 8:GA>G	c.1265del Ter	p.Lys422 frameshift_V ariant	-	89	154	80	459	108	73	F	-	0	0	0	0
7	11:276888 1:C>T	c.1552C>T Ter	p.Arg518 stop_gained	-	88	140	72	498	112	75	F	-	0	0	0	0
8	11:276888 1:C>T	c.1552C>T Ter	p.Arg518 stop_gained	-	74	112	100	466	92	21	F	-	0	0	0	0
9	11:252801 9:G>A	c.477+1G>A - Ter	- splice_donor variant	-	68	136	86	440	108	58	M	-	1	0	1	0

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10	11:276888	c.1552C>T	p.Arg518 Ter	stop_gained	-	82	124	68	457	42	76	F	-	0	0	0	0	
11	11:252801	c.477+1G>A	-	splice_variant	splice_donor	-	86	160	102	516	94	65	M	-	0	1	0	
12	11:252801	c.477+1G>A	-	splice_variant	splice_donor	-	76	144	74	463	98	65	F	-	0	0	0	
13	11:257071	9:GGCTG C,G	c.570_574del	p.Arg192 Cysteine	frameshift_V 1	frameshift_V alanine	-	118	-	100	515	0	85	M	-	0	0	1
14	11:277797	c.1733-1G>A	-	splice_acce prior_variant	splice_acce prior_variant	-	114	126	78	449	76	24	M	-	0	0	0	
15	11:206196	c.1394-1G>T	-	splice_acce prior_variant	splice_acce prior_variant	-	71	194	80	471	112	67	M	-	0	0	0	
16	11:276892	0:G,A	c.1590+1G>A	-	splice_donor prior_variant	-	85	186	86	452	106	74	M	-	0	0	0	
17	11:252794	2:TG;T	c.403del	p.Val135 SerfsTer1	frameshift_V 02	frameshift_V alanine	-	62	144	86	491	120	53	F	-	0	0	0
18	11:276891	7:C,T	c.1588C>T	p.Gln530 Ter	stop_gained &splice_regi on_variant	-	72	170	86	451	104	55	M	-	0	0	0	0
19	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	73	200	98	511	116	73	M	-	0	0	0	0
20	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	60	-	108	488	0	79	M	-	1	1	1	1
21	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	67	146	88	452	112	72	F	-	0	0	0	0
22	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	73	144	92	446	104	68	F	-	1	0	0	0
23	11:257140	4:G,A	c.683+1G>A	-	splice_donor prior_variant	-	56	144	76	457	68	86	F	-	0	0	0	0
24	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	73	128	82	511	0	85	F	-	0	0	0	0
25	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	60	132	88	504	100	60	F	-	0	0	0	0
26	11:277698	4:AG,A	c.1686del	p.Arg662 SerfsTer3	splice_acce prior_variant	-	83	198	88	493	116	68	F	-	0	0	0	0
27	11:257075	A	c.604_604+1i	p.Asp202 nsGTGA	frameshift_V 4	frameshift_V alanine	-	112	152	82	442	114	58	F	-	0	0	0
28	11:252799	1:CCT,C	c.451_452del	p.Leu151 GlyfsTer1	frameshift_V 33	frameshift_V alanine	-	62	196	88	487	108	44	F	-	0	0	0
29	11:257140	4:G,A	c.683+1G>A	-	splice_donor prior_variant	-	56	154	80	455	116	66	F	-	1	0	1	0
30	11:277802	3:C,T	c.1780C>T	p.Arg594 Ter	stop_gained	-	84	164	88	486	92	83	F	-	0	0	0	0
31	11:257071	9:GGCTG C,G	c.570_574del	p.Arg192 Cysteine	frameshift_V 1	frameshift_V alanine	-	99	130	78	510	92	46	F	-	0	0	0
32	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	77	158	82	432	90	41	M	-	0	0	0	0
33	11:277698	4:AG,A	c.1686del	p.Arg562 Ter	splice_acce prior_variant	-	78	172	72	451	112	32	F	-	0	0	0	0
34	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	86	134	74	485	98	56	F	-	0	0	0	0
35	11:276888	1:C,T	c.1552C>T	p.Arg518 Ter	stop_gained	-	81	150	82	466	110	57	F	-	0	0	0	0

36	11:258525 4:C:T	c.1075C>T	p.Gln359 Ter	stop_gained	-	72	166	90	462	116	62	F	-	0	0	0	0
37	9:GGCTG C:G	c.570_574del	p.Arg192 1	CysTer9	frameshift_v ariant	-	85	-	114	464	0	73	F	-	1	0	0
38	11:276888 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	73	180	82	451	112	67	M	-	0	0	0	0
39	11:26888 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	69	162	92	477	116	49	F	-	0	1	0	0
40	11:27688 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	62	134	80	487	112	74	F	-	1	1	0	0
41	11:252798 3:T:TA	c.443dup	p.Tyr148T Ter	stop_gained &frameshift_v ariant	-	66	170	80	436	100	60	F	-	0	0	0	0
42	11:277802 3:C:T	c.1780C>T	p.Arg594 Ter	stop_gained	-	80	162	92	456	104	52	F	-	0	0	0	0
43	11:258879 8:A:C:A	c.1380del	p.Pro448 Ter	frameshift_v ariant	8	-	72	174	80	455	100	32	F	-	0	0	0
44	11:266208 0:C:T	c.1513C>T	p.Gln505 Ter	stop_gained &splice_regi on_variant	-	67	162	76	521	116	77	F	-	1	0	0	0
45	11:276888 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	84	174	80	439	108	43	F	-	0	0	0	0
46	11:252801 9:G:A	c.477+1G>A	-	splice_donor variant	-	100	134	74	464	88	34	F	-	0	0	0	0
47	11:258530 5:C:T	c.1126C>T	p.Gln376 Ter	stop_gained &splice_regi on_variant	-	68	160	70	465	98	50	F	-	0	0	0	0
48	11:276888 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	84	204	90	477	92	82	M	-	1	0	0	0
49	11:27688 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	88	140	102	498	88	66	M	-	1	0	0	1
50	11:252794 2:TG:T	c.403del	p.Val135 SerTer1	frameshift_v ariant	02	-	85	134	118	476	74	29	M	-	0	0	0
51	11:276888 1:C:T	c.1552C>T	p.Arg518 Ter	stop_gained	-	53	192	106	472	124	78	M	-	1	0	0	0
1	7:1509503 36:G,A	c.2230C>T	p.Arg744 Ter	stop_gained	-	68	194	98	512	128	77	F	-	0	0	0	0
2	7:1509488 6:T:G,A	c.2567C>T	p.Arg863 Ter	stop_gained	-	58	158	86	469	128	73	M	-	0	0	0	0
3	7:1509510 40:G,A	c.2026C>T	p.Gln676 Ter	stop_gained	-	62	134	88	483	116	55	F	-	1	0	0	0
4	7:1509476 53:G,A	c.2917del	p.Leu973 Ter	frameshift_v ariant	-	98	140	76	457	94	37	F	-	0	0	0	0
5	7:1509510 82:T:G,T	c.1983del	p.Ile62S Ter	frameshift_v ariant	-	97	-	102	492	0	79	M	-	1	1	0	0
6	7:1509510 40:G,A	c.2026C>T	p.Gln676 Ter	stop_gained	-	95	152	84	482	112	53	M	-	0	0	0	0
7	7:1509779 0:CT:C	c.13del	p.Arg5Gly Ter	frameshift_v ariant	-	68	128	84	446	104	51	F	-	1	0	0	0
8	7:1509477 95:G;GC	c.2775dup	p.Pro926 Ter	frameshift_v ariant	4	-	92	130	76	460	108	64	F	-	0	0	0
9	7:1509473 87:ACA	c.3092del	p.Thr152 Ter	frameshift_v ariant	6	-	66	116	76	444	88	41	F	-	0	0	0
10	7:1509595 90:T:TG	c.453dup	p.Gly1031 Ter	frameshift_v ariant	80	-	68	164	102	472	110	52	M	-	0	0	0

KCNH2

Note: Variants are restricted to the canonical transcripts (ENST0000438793.7, PAM; ENST0000413689.5, SCN5A; ENST0000155840.10, KCNQ1; ENST0000262186.9, KCNH2); Lead, # lead in electrocardiogram; cDNA, c. cDNA consequence; protein.c, protein consequence; Csq, consequence,* combined consequence assuming variants on same allele; LOF, high-confidence loss-of-function; ECG, electrocardiogram; QC, quality control; PR, PR-interval duration; HR, heart rate; QRS, QRS-complex duration; QTc, Bazett correct QT-interval duration; PWD, P-wave duration; EUR, European; AFR, African; UND, undetermined; Anc, ancestry; BB, beta blocker usage; CCB, calcium channel blocker usage

Supplemental Table IX. Exome-wide significant associations from gene-based testing in TOPMed and replication in UK Biobank

			TOPMed			3 leads in UK Biobank			12 leads in UK Biobank			Meta UK Biobank			
ECG	Gene	Chr	N var	cMAC	P value	N var	cMAC	P value	N var	cMAC	P value	N var	cMAC	P value	
PR	PWD	STARD9	15	92	555	1.51E-06	-	-	-	34	91	0.193	-	-	-
		PAM	5	44	399	4.46E-07	44	554	0.02	21	184	0.37	38	738	0.016
		SCN5A	3	201	1089	7.62E-07	96	352	0.013	44	98	1.52E-04	115	450	4.40E-05
		BYSL	6	31	69	1.82E-07	14	26	0.92	7	10	0.744	16	36	0.79
		BAG6	6	10	13	4.62E-07	0	0	NA	0	0	NA	0	0	NA
		TMEM139	7	7	13	2.59E-07	6	12	0.24	1	1	0.804	6	13	0.24
		PRPF31	19	29	55	1.57E-06	3	6	0.07	2	3	0.395	3	9	0.13
QRS		IL17RD	3	21	27	5.58E-07	-	-	-	6	6	0.719	-	-	-
		LZTS1	8	6	14	2.06E-06	-	-	-	4	4	0.386	-	-	-
		SYBU	8	16	26	3.39E-06	-	-	-	7	8	0.170	-	-	-
		FBP1	9	27	93	9.03E-07	-	-	-	12	35	0.283	-	-	-
		HDHD3	9	15	26	2.70E-07	-	-	-	3	12	0.327	-	-	-
		IL11	19	6	10	7.89E-07	-	-	-	1	1	0.595	-	-	-
		KCNQ1	11	55	115	2.31E-12	24	56	1.10E-10	11	22	0.039	28	78	4.17E-11
QTc		KCNH2	7	63	319	3.18E-08	29	60	0.049	10	13	0.35	37	73	0.019
		OSBPL9	1	14	24	1.67E-08	8	12	0.21	3	4	0.753	10	16	0.23
		ZNF697	1	8	12	1.25E-09	9	200	0.93	3	67	0.351	9	267	0.98
		MFSD4A	1	16	121	3.67E-12	7	10	0.69	2	5	0.746	8	15	0.72
		MOB1B	4	10	14	5.10E-10	10	13	0.06	5	5	0.685	13	18	0.26
		ZFR	5	9	10	1.86E-11	3	148	0.49	2	55	0.683	3	203	0.46
		GPBP1	5	3	18	3.83E-08	4	25	0.06	1	2	0.715	4	27	0.06
		PPT2	6	15	17	2.23E-09	0	0	NA	0	0	NA	0	0	NA
		HDAC2	6	7	11	2.58E-09	3	15	0.77	1	3	0.030	3	18	0.96
		BIN3	8	11	23	8.50E-08	8	11	0.94	4	6	0.794	9	17	0.88
		NCOA2	8	10	16	5.93E-07	4	9	0.91	3	4	0.486	6	13	0.64
		E2F5	8	18	23	2.12E-06	5	40	0.23	2	15	0.939	6	55	0.43
		ZNF462	9	10	15	3.22E-07	7	14	0.11	1	2	0.412	7	16	0.09
		TMEM87A	15	11	16	2.12E-07	7	9	0.20	0	0	NA	7	9	NA
		DET1	15	23	28	1.16E-06	12	16	0.55	7	7	0.614	17	23	0.84
		KLHL10	17	13	22	4.42E-09	5	11	0.42	3	3	0.691	6	14	0.40
		OCSTAMP	20	16	24	2.21E-08	2	2	0.90	2	2	0.152	4	4	0.37
		FAM209B	20	5	12	2.26E-07	2	2	0.57	1	1	0.458	2	3	0.43

Chr: Chromosome, N var: the number of variants, cMAC: cumulative minor allele counts, PWD, P-wave duration; PR, PR interval; QRS, QRS duration; QTc, bazett corrected QT interval

Supplemental Table X. Results from gene-based testing for long-QT syndrome panel genes in TOPMed and UK Biobank

ECG	Gene	TOPMed			3-lead UK Biobank			12-lead UK Biobank			Meta UK Biobank		
		N var	cMAC	P value	N var	cMAC	P value	N var	cMAC	P value	N var	cMAC	P value
QTc	<i>KCNQ1</i>	55	115	2.31E-12	24	56	1.10E-10	11	22	0.039	28	78	4.17E-11
	<i>KCNH2</i>	63	319	3.18E-08	29	60	0.049	10	13	0.35	37	73	0.019
	<i>KCNE1</i>	9	29	1.24E-04	7	20	4.24E-04	4	4	0.04	8	24	9.03E-05
	<i>KCNJ2</i>	12	30	0.053	4	11	0.63	4	8	0.054	6	19	0.08
	<i>SCN5A</i>	196	1055	0.13	93	322	0.62	39	95	0.1	110	417	0.67
	<i>KCNE2</i>	19	326	0.19	6	293	1	5	105	0.2	8	398	0.6
	<i>CAV3</i>	11	127	0.4	6	11	0.48	3	3	0.4	7	14	0.88
	<i>KCNJ5</i>	32	61	0.51	16	34	0.13	9	12	0.55	22	46	0.48
	<i>SNTA1</i>	21	51	0.55	13	29	2.67E-03	8	8	0.48	17	37	0.02
	<i>SCN4B</i>	20	79	0.58	7	32	0.92	4	16	0.055	9	48	0.51
	<i>AKAP9</i>	45	188	0.88	33	754	0.13	18	272	0.44	42	1026	0.096
	<i>TRDN</i>	36	108	0.89	23	174	0.65	19	58	0.3	27	232	0.82
	<i>CALM2</i>	6	304	0.91	0	0	-	0	0	-	0	0	-
	<i>CACNA1C</i>	101	350	9	37	64	0.5	11	18	0.2	41	82	0.53
	<i>ANK2</i>	132	977	0.93	46	87	0.88	23	33	0.14	56	120	0.43
	<i>CALM3</i>	2	2	-	0	0	-	0	0	-	0	0	-
	<i>CALM1</i>	1	1	-	0	0	-	0	0	-	0	0	-

Note: QTc, Bazett-corrected QT; cMAC, cumulative minor allele count; meta, meta-analysis

Supplemental Table XI. Meta-analysis results for predicted-deleterious missense variants in *KCNE1* and QTc interval

<i>Individual cohort results</i>			TOPMed						3-lead UK Biobank			12-lead UK Biobank		
ECG	Groups	Gene	N carriers	beta	95%CI	P value	N carriers	beta	95%CI	P value	N carriers	beta	95%CI	P value
QTc	Predicted-deleterious missense	<i>KCNE1</i>	28	15.89	[7.75,24.03]	1.30E-04	20	15.29	[5.23, 25.34]	2.89E-03	4	19.67	[-4.1, 43.45]	1.00E-01
<i>Meta-analysis results</i>														
			meta UK Biobank						meta TOTAL					
			inverse-variance fixed effects						random effects (Paule-Mandel)					
ECG	Groups	Gene	N carriers	beta	95%CI	P value	N carriers	beta	95%CI	P value	beta	95%CI	P value	
QTc	Predicted-deleterious missense	<i>KCNE1</i>	24	15.95	[6.69, 25.21]	7.00E-03	52	15.92	[9.81, 22.03]	3.32E-07	15.92	[9.81, 22.03]	3.32E-07	

Note, QTc: Bazett correct QT-interval duration, beta: unit is ms, CI: confidence interval

Supplemental Table XII. Clinical characteristics of predicted-deleterious missense variant carriers of KCNE1 in TOPMed and UK Biobank

	Gene	Carrier #	Lead	QTc	variant	cDNA.c	protein.c	Csq	HR	PR	QRS	PWD	Age	Sex	Anc	BB	CCB	MI	HF
TOPMed																			
		1		403	21:34449343:G:A	c.292C>T	p.Arg98Trp	missense	66	120	153	88	65	F	EUR	0	0	0	0
		2		409	21:34449343:G:A	c.292C>T	p.Arg98Trp	missense	59	118	188	92	62	M	EUR	0	0	0	0
		3		420	21:34449343:G:A	c.292C>T	p.Arg98Trp	missense	60	118	197	96	70	F	EUR	0	0	0	0
		4		439	21:34449343:G:A	c.292C>T	p.Arg98Trp	missense	67	104	156	100	46	F	EUR	0	0	0	0
		5		474	21:34449343:G:A	c.292C>T	p.Arg98Trp	missense	89	148	206	112	62	M	EUR	0	0	0	0
		6		437	21:34449399:T:C	c.236A>G	p.Asn79Ser	missense	45	112	172	86	75	M	EUR	0	0	0	1
		7		426	21:34449409:C:T	c.226G>A	p.Asp76Asn	missense	57	92	142	84	47	F	EUR	0	0	0	0
		8		431	21:34449409:C:T	c.226G>A	p.Asp76Asn	missense	58	122	206	80	53	M	EUR	1	0	0	0
		9		459	21:34449409:C:T	c.226G>A	p.Asp76Asn	missense	76	106	154	80	53.6	F	EUR	0	0	0	0
		10		469	21:34449409:C:T	c.226G>A	p.Asp76Asn	missense	68	98	116	92	58.8	F	EUR	0	0	0	0
		11		477	21:34449409:C:T	c.226G>A	p.Asp76Asn	missense	55	124	202	94	40.9	F	AFR	0	NA	1	0
		12		495	21:34449409:C:T	c.226G>A	p.Asp76Asn	missense	69	120	162	80	73.4	F	AFR	0	0	0	0
		13		425	21:34449414:G:A	c.221C>T	p.Ser74Leu	missense	57	98	176	88	69	F	EUR	0	0	0	0
		14		486	21:34449430:T:C	c.205A>G	p.Lys69Glu	missense	76	114	168	100	48	M	EUR	0	0	1	0
		15	lead	394	21:34449435:C:T	c.200G>A	p.Arg67His	missense	60	100	194	94	67	M	EUR	0	0	0	0
		16		403	21:34449435:C:T	c.200G>A	p.Arg67His	missense	65	116	166	106	70	M	UND	0	0	0	0
		17		409	21:34449435:C:T	c.200G>A	p.Arg67His	missense	67	92	190	88	48	M	EAS	0	0	0	0
		18		416	21:34449435:C:T	c.200G>A	p.Arg67His	missense	67	98	126	88	68	F	AFR	0	0	0	0
		19		417	21:34449435:C:T	c.200G>A	p.Arg67His	missense	55	100	152	76	65	F	AFR	0	0	0	0
		20		420	21:34449435:C:T	c.200G>A	p.Arg67His	missense	73	110	150	78	65	F	EUR	0	0	0	0
		21		427	21:34449435:C:T	c.200G>A	p.Arg67His	missense	64	120	182	90	53	F	EUR	0	0	0	0
		22		434	21:34449435:C:T	c.200G>A	p.Arg67His	missense	65	108	164	88	53	F	EUR	0	0	0	0
		23		435	21:34449435:C:T	c.200G>A	p.Arg67His	missense	58	108	184	80	73.9	F	UND	0	1	0	0
		24		456	21:34449435:C:T	c.200G>A	p.Arg67His	missense	69	112	138	88	61	M	EUR	0	1	0	0
		25		467	21:34449435:C:T	c.200G>A	p.Arg67His	missense	67	126	174	88	72.1	F	AFR	0	0	0	0
		26		507	21:34449435:C:T	c.200G>A	p.Arg67His	missense	67	114	156	84	56.4	F	EUR	0	0	0	0
		27		420	21:34449436:G:T	c.199C>A	p.Arg67Ser	missense	49	108	158	86	57	F	UND	0	0	0	0
		28		449	21:34449463:T:G	c.172A>C	p.Thr58Pro	missense	64	96	134	74	72	F	UND	0	0	0	0
UK Biobank																			
KCNEN1	1	3-lead	410	21:34449435:C:T	c.200G>A	p.Arg67His	missense	73	150	76	72	54	F	EUR	0	0	0	0	
KCNEN1	2	3-lead	465	21:34449435:C:T	c.200G>A	p.Arg67His	missense	82	196	98	76	61	M	EUR	1	0	0	0	

3	3-lead	409	21:34444435:C:T	c.200G>A	p.Arg67His	missense	58	144	128	80	52	M	EUR	0	0	0	0	0
4	12-lead	430	21:344449435:C:T	c.200G>A	p.Arg67His	missense	47	184	98	70	50	F	EUR	0	0	0	0	0
5	12-lead	425	21:344449435:C:T	c.200G>A	p.Arg67His	missense	73	154	78	94	56	F	EUR	0	0	0	0	0
6	3-lead	428	21:344449459:A:G	c.176T>C	p.Leu59Pro	missense	64	144	86	100	55	M	EUR	0	0	0	0	0
7	3-lead	395	21:344449459:A:G	c.176T>C	p.Leu59Pro	missense	53	150	86	98	53	M	EUR	0	0	0	0	0
8	12-lead	477	21:344449459:A:G	c.176T>C	p.Leu59Pro	missense	59	194	82	116	63	M	EUR	0	0	0	0	0
6	3-lead	428	21:344449463:T:G	c.172A>C	p.Thr58Pro	missense	64	144	86	100	55	M	EUR	0	0	0	0	0
8	12-lead	477	21:344449463:T:G	c.172A>C	p.Thr58Pro	missense	59	194	82	116	63	M	EUR	0	0	0	0	0
9	3-lead	451	21:344449469:A:G	c.166T>C	p.Phe56Leu	missense	70	134	148	86	57	M	EUR	0	0	1	0	0
10	12-lead	428	21:344449469:A:G	c.166T>C	p.Phe56Leu	missense	58	230	84	76	64	F	EUR	1	0	0	0	0
11	3-lead	420	21:344449343:G:A	c.292C>T	p.Arg98Trp	missense	71	128	88	94	56	F	EUR	0	0	0	0	0
12	3-lead	452	21:344449343:G:A	c.292C>T	p.Arg98Trp	missense	84	160	96	118	50	M	EUR	0	0	0	0	0
13	3-lead	467	21:344449343:G:A	c.292C>T	p.Arg98Trp	missense	78	124	100	82	57	M	EUR	0	0	0	0	0
14	3-lead	446	21:344449343:G:A	c.292C>T	p.Arg98Trp	missense	60	122	88	88	57	F	EUR	0	0	0	0	0
15	3-lead	487	21:344449343:G:A	c.292C>T	p.Arg98Trp	missense	88	114	104	86	44	F	EUR	0	1	0	0	0
16	12-lead	439	21:344449343:G:A	c.292C>T	p.Arg98Trp	missense	64	144	82	80	70	F	EUR	0	0	0	0	0
17	3-lead	396	21:344449414:G:A	c.221C>T	p.Ser74Leu	missense	63	112	88	84	48	F	EUR	0	0	0	0	0
18	3-lead	430	21:344449414:G:A	c.221C>T	p.Ser74Leu	missense	60	124	98	84	53	F	EUR	0	0	0	0	0
19	3-lead	457	21:344449436:G:T	c.199C>A	p.Arg67Ser	missense	79	134	124	108	54	F	EUR	1	0	0	0	0
20	3-lead	438	21:344449436:G:T	c.199C>A	p.Arg67Ser	missense	96	150	70	94	56	F	EUR	0	0	0	0	0
21	3-lead	427	21:344449436:G:T	c.199C>A	p.Arg67Ser	missense	72	174	88	102	59	F	EUR	0	0	0	0	0
22	3-lead	419	21:344449436:G:T	c.199C>A	p.Arg67Ser	missense	83	110	152	62	49	F	EUR	0	0	0	0	0
23	3-lead	454	21:344449436:G:T	c.199C>A	p.Arg67Ser	missense	79	138	152	104	57	F	EUR	0	0	0	0	0
24	3-lead	429	21:344449436:G:T	c.199C>A	p.Arg67Ser	missense	78	126	70	88	58	M	EUR	0	0	0	0	0
25	12-lead	422	21:344449436:G:T	c.199C>A	p.Arg67Ser	missense	56	184	74	108	67	F	EUR	1	0	0	0	0

Note: Variants are restricted to the canonical transcript (ENST00000337385.7, KCNE1);^LLead , # lead in electrocardiogram; cDNA_c, cDNA consequence; protein_c, protein consequence; Csq, consequence; QC, quality control; PR, PR-interval duration; HR, heart rate; QRS, QRS-complex duration; QTc, Bazett correct QT-interval duration; PWD, P-wave duration; Anc, ancestry; BB, beta blocker usage; CCB, calcium channel blocker usage

Supplemental Table XIII. Clinical characteristics of likely pathogenic and pathogenic variant carriers in LQTS genes in TOPMed and UK Biobank

Gene	CARRIER #	Passed d QTc exclusi ons	Passed d PR exclusi ons	QT variant	cDNA.c	protein.c	significance	Phenotype	HR	PWD	PR	QRS	Age	Sex	Anc	BB	CCB	MII	HF
TOPMed																			
1	12- lea d	YES	NA	436	11:2445251:C :G	c.153C>G	p.Tyr51T er	Pathogenic	Long QT syndrome;not provided	70	114	182	92	49.7	M	EUR	0	0	0
2	12- lea d	YES	NA	464	11:2445251:C :G	c.153C>G	p.Tyr51T er	Pathogenic	Long QT syndrome;not provided	63	136	190	100	79.2	M	EUR	0	1	0
3	12- lea d	YES	NA	458	11:2445294:T C>T	c.200delC	p.Pro67A rgfs	Pathogenic	Long QT syndrome	73	96	132	86	54.0	F	AFR	0	0	0
4	12- lea d	YES	NA	474	11:2570670:C :T	c.520C>T	p.Arg174 Cys	Pathogenic	Congenital long QT syndrome;Lon g QT syndrome	57	98	162	88	54.0	F	EUR	0	0	0
5	12- lea d	YES	NA	473	11:2570718:C :T	c.568C>T	p.Arg190 Trp	Likely pathogenic	Cardiovascular phenotype;Con genital long QT syndrome;Lon g QT syndrome	58	108	158	86	57.0	M	EUR	0	0	0
6	12- lea d	YES	NA	511	11:2570719: G:A	c.569G>A	p.Arg190 Gln	Pathogenic	Cardiovascular phenotype;Con genital long QT syndrome;Lon g QT syndrome	73	118	168	68	69.0	F	EUR	0	0	1
7	12- lea d	YES	NA	480	11:2570719: GGCTGC:G	c.573_577d elGGCGCT	p.Arg192 Cysfs	Pathogenic	1;not provided Cardiovascular phenotype;Jer vell and Lange-Nielsen syndrome;Jer ell and Lange- Nielsen syndrome	66	98	188	90	51.0	F	EUR	0	0	0
8	12- lea d	YES	NA	424	11:2570719: GGCTGC:G	c.573_577d elGGCGCT	p.Arg192 Cysfs	Pathogenic	1;Long QT syndrome;not provided Cardiovascular phenotype;Jer vell and Lange-Nielsen syndrome;Jer ell and Lange- Nielsen syndrome	61	132	170	82	73.0	F	EUR	0	0	0
9	12- lea d	YES	NA	477	11:2570742:A :G	c.592A>G	p.Ile198V al	Pathogenic	Congenital long QT	70	56	150	96	60.0	F	EUR	0	0	1

24	12-lea d	YES	NA	467	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
22	12-lea d	YES	NA	444	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
23	12-lea d	YES	NA	445	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
24	12-lea d	YES	NA	410	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
25	12-lea d	YES	NA	444	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
26	12-lea d	YES	NA	453	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
27	12-lea d	YES	NA	469	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
28	12-lea d	YES	NA	451	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
29	12-lea d	YES	NA	419	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
30	12-lea d	YES	NA	453	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
31	12-lea d	YES	NA	432	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA
32	12-lea d	YES	NA	424	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	1	0	1	NA
33	12-lea d	YES	NA	439	11:2571391:C ;T	c.671C>T	p.Thr224 Met*	Likely pathogenic	Congenital long QT syndrome;Lon g QT syndrome	Amis h	0	0	0	NA

34	12- d	lea	YES	NA	473	11:2571408: G,A	c.683+5G>	NA	Pathogenic	not provided	69	124	160	76	58.6
35	12- d	lea	YES	NA	470	11:2571408: G,A	c.683+5G> A	NA	Pathogenic	not provided	72	86	122	86	35.0
36	12- d	lea	YES	NA	488	11:2572858:A C,A	c.796delC	p.Leu266 Cysfs	Pathogenic	Long QT syndrome; 1;not provided	60	108	160	90	64.0
37	12- d	lea	YES	NA	453	11:2572858:A C,A	c.796delC	p.Leu266 Cysfs	Pathogenic	Long QT syndrome; 1;not provided	58	104	156	68	64.0
38	12- d	lea	YES	NA	454	11:2572871: G,A	c.806G>A	p.Gly269 Asp	Pathogenic	Congenital long QT syndrome;Lon g QT syndrome;Lon g QT syndrome	58	110	142	84	66.3
39	12- d	lea	YES	NA	493	11:2572871: G,A	c.806G>A	p.Gly269 Asp	Pathogenic	1;not provided Congenital long QT syndrome;Lon g QT syndrome;Lon g QT syndrome	49	120	160	104	75.0
40	12- d	lea	YES	NA	402	11:2572895:C ;T	c.830C>T	p.Ser277 Leu	Pathogenic	Cardiovascular phenotype;Con genital long QT syndrome;Lon g QT syndrome;not provided	54	100	188	90	46.0
41	12- d	lea	YES	NA	480	11:2583545: G,A	c.1032G>A	p.Ala344 =	Pathogenic	Cardiovascular phenotype;Con genital long QT syndrome;Lon g QT syndrome;Lon g QT syndrome;Lon g QT syndrome;Lon g QT syndrome;not provided	49	94	146	94	47.0
42	12- d	lea	YES	NA	515	11:2583546: G,A	c.1032+1G>	NA	Likely pathogenic	2;not provided Long QT syndrome;not provided	89	NA	NA	82	79.0
43	12- d	lea	YES	NA	432	11:258364:A ;G	c.1085A>G	p.Lys362 Arg	Pathogenic	Abnormality of the cerebral white matter;Abnor mality of the nerves;Atrial fibrillation, familial, 3;Beckwith- Wiedemann syndrome;Con genital long QT syndrome;Con genital microcephaly; Decreased fetal movement;Diff use white	53	132	210	106	57.6

sinal
microcephaly:
Short QT
syndrome
2;Toe
climodactyly;no
t provided

45	12- d	lea	YES	NA	440	11:2587631: G,A	c.1190G>A	p.Arg397 Gln	Likely pathogenic	not provided	73	122	186	78	52.0	F	EUR	0	1	0	1
46	12- d	lea	YES	NA	406	11:2587631: G,A	c.1190G>A	p.Arg397 Gln	Likely pathogenic	not provided	62	96	202	90	75.8	M	EUR	0	0	0	0
47	12- d	lea	YES	NA	419	11:2587631: .5	c.1190G>A	p.Arg397 Gln	Likely pathogenic	not provided	66	94	173	96	73.0	F	EUR	0	0	0	0
48	12- d	lea	YES	NA	419	11:2587636: G,GC	c.1201dupC	p.Arg401 Profs	Pathogenic	Cardiovascular phenotype;not provided	54	102	156	86	45.3	M	EUR	0	0	0	0
49	12- d	lea	YES	NA	449	11:2587636: G,GC	c.1201dupC	p.Arg401 Profs	Pathogenic	Cardiovascular phenotype;not provided	71	118	164	106	68.3	M	EUR	0	1	0	0

50	12- d	lea	YES	NA	494	11:276881:C ;T	c.1552C>T	p.Arg1518 Ter	Pathogenic	Atrial fibrillation, familial, 3;Beckwith- Wiedemann syndrome;Car- diovascular phenotype;Jer- sey耳垂 Lange-Nielsen syndrome;Lon- g QT syndrome 1;Long QT syndrome 1, recessive;not provided	55	120	162	86	63.3	F	UND	0	0	0	0
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51	12- d	lea	YES	NA	445	11:2768917:C ;T	c.1588C>T	p.Gln530 Ter	Pathogenic	Atrial fibrillation, familial, 3;Beckwith- Wiedemann syndrome;Car- diovascular phenotype;Jer- sey耳垂 Lange-Nielsen syndrome;Lon- g QT syndrome 1;Short QT syndrome 2;not provided	55	112	198	92	55.0	M	EUR	0	0	0	0
52	12- d	lea	YES	NA	427	11:2776984:A ;G	c.1686- 2A>G	N/A	Likely pathogenic	Cardiovascular phenotype;Jer- sey耳垂 syndrome 1;not provided	64	NA	182	90	49.8	M	SAS	1	1	1	NA

KCNJ2										
	1	12-lea d	YES	NA	441	17:70175239: G,A	c.200G>A	p.Arg67 Gln	Pathogenic	Congenital long QT syndrome;not provided;not specified
KCNE2	1	12-lea d	YES	NA	466	21:34370825: C,T	c.347C>T	p.Ala116 Val	Likely pathogenic	Acquired long QT syndrome;not provided
	2	12-lea d	YES	NA	426	21:34370825: C,T	c.347C>T	p.Ala116 Val	Likely pathogenic	Acquired long QT syndrome;not provided
SCN5A	1	12-lea d	YES	YES	509	3:38551022:C ;T	c.5350G>A	p.Glu178 4Lys	Pathogenic	Brugada syndrome;Brug ada syndrome 1;Cardiovascul ar phenotype;Con genital long QT syndrome;Lon g QT syndrome 1;Long QT syndrome 3;Sinus node disease;not provided
	2	12-lea d	YES	YES	415	3:38551145:C ;T	c.5227G>A	p.Gly174 3Arg	Pathogenic	Brugada syndrome;Brug ada syndrome 1;Cardiovascul ar phenotype;Con genital long QT syndrome;Lon g QT syndrome 1;Long QT syndrome 3;Sinus node disease;not provided
SCN5A	3	12-lea d	YES	YES	401	3:38551243: G,A	c.5126C>T	p.Ser170 9Leu	Pathogenic	Brugada syndrome;Bug ada syndrome 1;Cardiovascul ar phenotype;Par oxysmal familial ventricular fibrillation 1;Ventricular fibrillation;not provided
	4	12-lea d	YES	YES	515	3:38551441:C ;T	c.4931G>A	p.Arg164 4His	Pathogenic	Brugada syndrome;Car diovascular phenotype;Con genital long QT syndrome;Lon g QT syndrome 3;not provided
SCN5A	5	12-lea d	YES	YES	404	3:38551519: GAGA;G	c.4850_485 2delCT	p.Phe16 17del	Likely pathogenic	Brugada syndrome;Lon g QT syndrome 1;Long QT syndrome;Lon g QT syndrome 3;not provided
	6	12-lea d	YES	YES	363	3:38562422:C ;A	c.3956G>T	p.Gly131 9Val	Likely pathogenic	Brugada syndrome;Car diovascular phenotype;Lon g QT syndrome 3;not provided

24	12-lea d	YES	YES	385	3:38606682:C ;T	c.1127G>A	p.Arg376 His	Pathogenic	Brugada Syndrome;Car diovascular phenotype;not provided	52	148	164	86	51.5	M	AFR	0	0	0	0
1	12-lea d	YES	NA	425	3:8733882:G ;G	c.10_17del GAAGAAGA; A	p.Glu4Hi sfs	Pathogenic	Long QT syndrome;not provided	68	102	144	92	53.0	F	AFR	0	0	0	0
2	12-lea d	YES	NA	416	3:8745580:G; A	c.169G>A	p.Val57M et	Likely pathogenic	Long QT syndrome;not provided	57	112	170	100	54.0	M	EUR	0	0	0	1
3	12-lea d	YES	NA	448	3:8745580:G; A	c.169G>A	p.Val57M et	Likely pathogenic	Long QT syndrome;not provided	72	102	140	98	55.0	F	EUR	0	0	0	0
1	12-lea d	YES	NA	399	6:123255098: A,C	c.1934T>G	p.Leu645 Ter	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia	63	116	164	88	51.1	M	EUR	1	0	0	0
2	12-lea d	YES	NA	428	6:123255098: A,C	c.1934T>G	p.Leu645 Ter	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia	65	NA	NA	106	81.4	M	EUR	0	0	0	0
3	12-lea d	YES	NA	414	6:123255869: TTTC:T	c.1900_190 3delGAAA	p.Glu634 Lysfs	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	61	124	174	86	55.0	F	AFR	0	0	0	0
4	12-lea d	YES	NA	411	6:123255869: TTTC:T	c.1900_190 3delGAAA	p.Glu634 Lysfs	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	59	120	168	98	32.6	F	AFR	0	1	0	0
5	12-lea d	YES	NA	405	6:123255869: TTTC:T	c.1900_190 3delGAAA	p.Glu634 Lysfs	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	54	NA	118	80	75.0	F	AFR	1	0	NA	NA
6	12-lea d	YES	NA	418	6:123255869: TTTC:T	c.1900_190 3delGAAA	p.Glu634 Lysfs	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	71	120	160	100	52.6	F	AFR	0	1	0	0
7	12-lea d	YES	NA	475	6:123255869: TTTC:T	c.1900_190 3delGAAA	p.Glu634 Lysfs	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	63	116	160	92	66.2	F	AFR	1	0	1	0
8	12-lea d	YES	NA	458	6:123255869: TTTC:T	c.1900_190 3delGAAA	p.Glu634 Lysfs	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	65	140	212	102	58.6	F	UND	0	0	0	0
9	12-lea d	YES	NA	437	6:123255869: TTTC:T	c.1900_190 3delGAAA	p.Glu634 Lysfs	Pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	77	136	154	94	63.6	M	UND	0	0	0	0

TRDN

21	12-lea-d	YES	NA	416	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	72	98	132	84	50.0 F EUR 0 0 0 0
22	12-lea-d	YES	NA	416	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	57	108	142	90	60.7 M EUR 0 0 0 0
23	12-lea-d	YES	NA	422	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	72	112	186	120	57.0 M EUR 0 0 1 1
24	12-lea-d	YES	NA	402	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	53	118	215	100	67.0 M EUR 0 0 0 0
25	12-lea-d	YES	NA	465	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	66	102	130	82	59.0 F EUR 0 0 0 0
26	12-lea-d	YES	NA	402	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	65	114	168	102	43.6 F UND 0 0 0 0
27	12-lea-d	YES	NA	413	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	69	106	192	100	51.0 M EUR 0 0 0 0
28	12-lea-d	YES	NA	418	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	62	114	136	80	53.1 F EUR 0 0 0 0
29	12-lea-d	YES	NA	418	6:123366174:G,A	c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	67	100	140	84	73.4 F EUR 0 0 0 0
30	12-lea-d	YES	NA	410	6:123366174:c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	75	112	156	90	67.0 F EUR 0 0 0 0	
31	12-lea-d	YES	NA	419	6:123366174:c.1282C>T	p.Arg428Ter	Likely pathogenic	Catecholamine rgic polymorphic ventricular tachycardia;not provided	63	94	138	82	54.0 M EUR 1 0 0 1	

32	12-lea d	YES	NA	412. 2	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	65	114	178	92	65.0 M EUR 0 0 0 0
33	12-lea d	YES	NA	462	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	75	114	134	86	52.1 F EUR 0 0 0 0
34	12-lea d	YES	NA	444	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	70	NA	166	98	75.2 M EUR 1 1 NA NA
35	12-lea d	YES	NA	429. 3	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	75	114	153	100	72.0 F AFR 0 1 0 0
36	12-lea d	YES	NA	410	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	62	102	166	84	68.0 F UND 0 0 0 0
37	12-lea d	YES	NA	417	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	69	106	172	82	66.3 F EUR 0 0 0 0
38	12-lea d	YES	NA	414	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	64	120	160	80	75.0 F EUR 0 0 0 0
39	12-lea d	YES	NA	460	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	73	118	168	90	67.2 F EUR 0 0 0 0
40	12-lea d	YES	NA	428	6:123366174: G.A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	71	108	144	92	46.0 F EUR 0 0 0 0
41	12-lea d	YES	NA	425	6:12337727: T.TTC	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Catecholamine rgic	69	114	158	104	63.8 M AFR 0 0 1 1
42	12-lea d	YES	NA	442	6:123438062: C.T	c.1051+1G> A	NA	Likely pathogenic	Catecholamine rgic	68	110	162	86	65.0 F EUR 0 0 0 1

43	12-lea d	YES	NA	434	6:12350389:	G.A	c.613C>T	p.Gln205 Ter	Pathogenic	tachycardia;Ve ntricular catecholaminer glc	81	104	160	94	38.5	M	EUR	0	0	0																
44	12-lea d	YES	NA	427	6:12350389:	G.A	c.613C>T	p.Gln205 Ter	Pathogenic	tachycardia, 5, with or without muscle weakness;not provided	polymorphic, 5, with or without muscle weakness;not provided	rgic	polymorphic	ventricular	tachycardia;Ve ntricular catecholaminer glc	12-lea d	YES	NA	434	6:12350389:	G.A	c.613C>T	p.Gln205 Ter	Pathogenic	tachycardia;Ve ntricular catecholaminer glc	81	104	160	94	38.5	M	EUR	0	0	0	0
45	12-lea d	YES	NA	353	6:12350389:	G.A	c.613C>T	p.Gln205 Ter	Pathogenic	tachycardia;Ve ntricular catecholaminer glc	50	112	158	98	39.0	M	EUR	0	0	0	0															
46	12-lea d	YES	NA	447	6:12350389:	G.A	c.613C>T	p.Gln205 Ter	Pathogenic	tachycardia; ntricular catecholaminer glc	70	120	158	80	75.1	F	EUR	0	0	0	0															
47	12-lea d	YES	NA	404	6:12350389:	G.A	c.613C>T	p.Gln205 Ter	Pathogenic	tachycardia; ntricular catecholaminer glc	83	98	162	68	63.0	F	AfR	0	0	0	1															

KCNE2																					
53	12- lea d	YES	NA	427	6:12357:1098: GCTGT:G	c.53_56del ACAG	p.Asp18 Alafs	Pathogenic	tachycardia,Ve ntricular catecholaminer gic	70	122	180	84	79.0	M	AFR	0	0	0	1	
54	12- lea d	YES	NA	463	6:12357:1098: GCTGT:G	c.53_56del ACAG	p.Asp18 Alafs	Pathogenic	tachycardia,Ve ntricular catecholaminer gic	70	122	180	84	79.0	M	AFR	0	0	0	1	
									polymorphic, 5, with or without muscle weakness												
									Catecholamine ergic												
									polymorphic ventricular tachycardia,Ve ntricular catecholaminer gic	118	118	218	80	55.9	F	AFR	0	NA	0	0	
									polymorphic, 5, with or without muscle weakness												
									Catecholamine ergic												
									polymorphic ventricular tachycardia,Ve ntricular catecholaminer gic	68	112	186	88	54.0	F	AFR	1	1	0	0	
									polymorphic, 5, with or without muscle weakness												
									Long QT syndrome;not provided	54	118	180	106	45.1	M	AFR	0	0	0	0	
									Congenital long QT syndrome;1 9 QT syndrome 2,not provided	70	114	209	84	66.0	F	AFR	0	0	0	0	
									Congenital long QT syndrome;1 9 QT syndrome 2,not provided	61	106	180	106	62.0	M	EAS	0	0	0	0	
									Long QT syndrome;not provided	77	116	170	86	63.7	M	EUR	0	0	0	0	
4	12- lea d	YES	NA	531	7:150947724: G:GGCCCC	8dupGGGG C	p.Arg910 Argfs	Pathogenic	syndrome;not provided	77	116	170	86	63.7	M	EUR	0	0	0	0	
5	12- lea d	YES	NA	504	7:150947724: G:GGCCCC	c.2724_272 8dupGGGG C	p.Pro910 Argfs	Pathogenic	syndrome;not provided	42	102	188	110	37.0	M	EUR	0	0	0	0	

6	12-lea-d	YES	NA	478	7:150947842: G:GGCCC	c.2724_2728dupGGGG C	p.Pro910Argfs	Pathogenic	Long QT syndrome;not provided	52	100	174	78	63.5	F	EUR	0	0	0	0	0
7	12-lea-d	YES	NA	465	7:150950311: C-T	c.2255G>A	p.Arg752Gln	Likely pathogenic	Congenital long QT syndrome;Lion syndrome;Lion g QT syndrome;Romano-Ward syndrome;not provided	66	120	150	80	63.0	F	EUR	0	0	0	0	0
8	12-lea-d	YES	NA	482	7:150950312: G,A	c.2254C>T	p.Arg752Trp	Pathogenic	Cardiovascular phenotype;Congenital long QT syndrome;Lion syndrome;Romano-Ward syndrome;not provided	71	94	160	90	69.0	F	AMR	0	0	0	0	0
9	12-lea-d	YES	NA	418	7:150955469: CCT:G	c.1128+18_0_21del	p.Arg752Glyfs	Likely pathogenic	Long QT syndrome;Short QT syndrome	56	116	172	90	71.0	F	EUR	0	1	0	0	0
10	12-lea-d	YES	NA	471	7:150955481: G,A	c.1128+18_0C>T	p.Arg752Glyfs	Likely pathogenic	Long QT syndrome;Short QT syndrome	71	116	134	94	50.0	F	EUR	0	0	1	1	1
11	12-lea-d	YES	NA	437	7:150955481: G,A	c.1128+18_0C>T	p.Arg752Glyfs	Likely pathogenic	Long QT syndrome;Short QT syndrome	85	112	130	90	59.0	F	EUR	0	0	0	0	0
UK Biobank																					
CAV3																					
1	12-lea-d	YES	NA	428	3:8745580:G-	c.169G>A	p.Val57Mfs	Likely pathogenic	Long QT syndrome;not provided	46	138	86	108	48	F	EUR	0	0	0	0	0
1	3-lea-d	YES	YES	417	3:38550545:G-C	c.5825_5826delCT	p.Pro1942Argfs	Likely pathogenic	not provided	58	192	90	90	47	M	EUR	0	0	0	0	0
2	3-lea-d	YES	YES	425	3:38550545:C	c.5825_5826delCT	p.Pro1942Argfs	Likely pathogenic	not provided	65	150	100	86	49	F	EUR	0	0	0	0	0
3	3-lea-d	NO	YES	458	3:38550545:C	c.5825_5826delCT	p.Pro1942Argfs	Likely pathogenic	not provided	77	98	98	292	57	F	EUR	0	0	0	0	0
SCN5A																					
4	3-lea-d	YES	YES	408	3:38551505:G,A	c.4867C>T	p.Arg162Ter	Pathogenic	Cardiovascular phenotype; Long QT syndrome 3; Sick sinus syndrome 1, autosomal recessive; not provided	52	170	104	116	50	F	EUR	0	0	0	0	0

5	3- lea d	YES	YES	410	3:38551519: GAGA:G	c.4850_485 2delCT	p.Phe616 17del	Likely pathogenic	Brugada syndrome; Long QT syndrome; Long QT Syndrome 3; not provided	63	184	110	76	58
6	3- lea d	YES	YES	363	3:38581266: G.A	c.2893C>T	p.Arg965 Cys	Pathogenic	Brugada syndrome; not provided	63	154	68	78	52
7	3- lea d	YES	YES	389	3:38597737:C :T	c.2254G>A	p.Gly752 Arg	Pathogenic	Brugada syndrome; Cardiovascular phenotype; not provided	61	148	116	96	43
8	3- lea d	YES	YES	470	3:38614063:A :C	c.615T>G	p.Tyr205 Ter	Pathogenic	Atrial fibrillation; familial 10; Brugada syndrome 1; Dilated cardiomyopath y (IE; Long QT syndrome 3; SCN5A- Related Disorders	73	152	94	92	52
9	3- lea d	YES	YES	389	3:38614063:A :C	c.615T>G	p.Tyr205 Ter	Pathogenic	Atrial fibrillation; familial 10; Brugada syndrome 1; Dilated cardiomyopath y (IE; Long QT syndrome 3; SCN5A- Related Disorders	51	178	84	68	57
10	3- lea d	YES	YES	435	3:38614063:A :C	c.615T>G	p.Tyr205 Ter	Pathogenic	Atrial fibrillation; familial 10; Brugada syndrome 1; Dilated cardiomyopath y (IE; Long QT syndrome 3; SCN5A- Related Disorders	71	180	82	94	47
11	3- lea d	NO	YES	427	3:38603999: G.A	c.1603C>T	p.Arg535 Ter	Pathogenic/Li kely pathogenic	Brugada syndrome;Car diovascular phenotype	80	138	180	124	59
12	3- lea d	YES	YES	420	3:38630341:C :T	c.362G>A	p.Arg121 Gln	Pathogenic	Brugada syndrome	60	104	74	78	54
13	12- lea d	YES	YES	381	3:38551502:C :T	c.4870G>A	p.Val162 4le	Likely pathogenic	not provided	66	172	72	100	75
14	12- lea d	YES	YES	396	3:38560260:C :T	c.4132G>A	p.Val137 8Met	Likely pathogenic	Brugada syndrome	59	200	92	134	49

15	12-lea-d	YES	YES	470	3:38562404;C	c.3988G>A	p.Arg133Thr	Pathogenic / Likely pathogenic	Cardiovascular phenotype; Congenital long QT syndrome; SCN5A-related disorder; not provided	60	174	88	102	66	M	EUR	0	0	0
16	12-lea-d	YES	YES	406	3:38562470;C	c.3908G>A	p.Arg130Gln	Likely pathogenic	Atrial fibrillation; familial, 10; Brugada Syndrome 1; Dilated cardiomyopathy; Long QT syndrome; SCN5A-Related Disorders	84	150	78	100	67	F	EUR	0	0	0
17	12-lea-d	YES	YES	403	3:38566408;C	c.3840+1G>A	NA	Pathogenic / Likely pathogenic	Brugada syndrome; not provided	63	238	90	98	71	M	EUR	0	0	0
18	12-lea-d	YES	YES	420	3:38614063;A	c.615T>G	p.Tyr205Ter	Pathogenic	Atrial fibrillation; familial, 10; Brugada Syndrome 1; Dilated cardiomyopathy; Long QT syndrome; SCN5A-Related Disorders	60	174	94	92	52	F	EUR	0	0	0
19	12-lea-d	YES	YES	399	3:38614063;A	c.615T>G	p.Tyr205Ter	Pathogenic	Atrial fibrillation; familial, 10; Brugada Syndrome 1; Dilated cardiomyopathy; Long QT syndrome; SCN5A-Related Disorders	67	148	74	98	66	F	EUR	0	0	0
20	12-lea-d	YES	YES	435	3:38614063;A	c.615T>G	p.Tyr205Ter	Pathogenic	Atrial fibrillation; familial, 10; Brugada Syndrome 1; Dilated cardiomyopathy; Long QT syndrome; SCN5A-Related Disorders	68	168	82	96	68	F	EUR	0	0	0
21	12-lea-d	YES	YES	412	3:38614063;A	c.615T>G	p.Tyr205Ter	Pathogenic	Atrial fibrillation; familial, 10; Brugada Syndrome 1; Dilated cardiomyopathy; Long QT syndrome; SCN5A-Related Disorders	60	132	82	94	74	F	EUR	0	0	0
22	12-lea-d	YES	YES	394	3:38614063;A	c.615T>G	p.Tyr205Ter	Pathogenic	Atrial fibrillation; familial, 10; Brugada	60	214	98	120	59	F	EUR	0	0	0

5	3-lea d	YES	NA	411	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	tachycardia; not provided					
6	3-lea d	YES	NA	431	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	74	130	88	94	41 M EUR 0 0 0 0
7	3-lea d	YES	NA	400	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	74	122	70	88	56 M EUR 0 0 0 0
8	3-lea d	YES	NA	367	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	76	116	94	82	54 F EUR 0 0 0 0
9	3-lea d	YES	NA	458	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	58	124	78	68	50 F EUR 0 0 0 0
10	3-lea d	YES	NA	383	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	68	170	68	64	52 F EUR 0 0 0 0
11	3-lea d	YES	NA	460	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	68	126	106	72	58 F EUR 0 0 0 0
12	3-lea d	YES	NA	419	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	83	142	70	78	45 M EUR 0 0 0 0
13	3-lea d	YES	NA	431	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	71	128	90	98	48 M EUR 0 0 0 0
14	3-lea d	YES	NA	396	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	65	120	92	78	50 M EUR 0 0 0 0
15	3-lea d	YES	NA	429	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	rgic polymorphic ventricular tachycardia; not provided	69	140	74	102	57 M EUR 0 1 0 0

16	3-lea d	YES	NA	386	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	tachycardia; not provided				
17	3-lea d	YES	NA	416	6:123366174: G:A	c.1282C>T	p.Arg428 Ter	Likely pathogenic	Likely pathogenic	Catecholamine	tachycardia; not provided				
18	3-lea d	YES	NA	434	6:123438062: C:T	c.1051+1G>A	NA	Likely pathogenic	Likely pathogenic	Catecholamine	tachycardia; not provided				
19	3-lea d	YES	NA	462	6:12350389: G,A	c.613C>T	p.Gln205 Ter	Pathogenic	Ventricular tachycardia; catecholaminergic polymorphic, 5, with or without muscle weakness; not provided	Catecholamine	tachycardia; not provided				
20	3-lea d	YES	NA	463	6:12350389: G,A	c.613C>T	p.Gln205 Ter	Pathogenic	Ventricular tachycardia; catecholaminergic polymorphic, 5, with or without muscle weakness; not provided	Catecholamine	tachycardia; not provided				
21	3-lea d	YES	NA	406	6:12350389: G,A	c.613C>T	p.Gln205 Ter	Pathogenic	Ventricular tachycardia; catecholaminergic polymorphic, 5, with or without muscle weakness; not provided	Catecholamine	tachycardia; not provided				
22	3-lea d	YES	NA	397	6:12350389: G,A	c.613C>T	p.Gln205 Ter	Pathogenic	Ventricular tachycardia; not provided	Catecholamine	tachycardia; not provided				

23	12-lea d	YES	NA	436	6:123366174: G,A	c.1282C>T	p.Arg428 Ter	Pathogenic / Likely pathogenic	Catecholamine Igic	Pathogenic / polymorphic ventricular tachycardia; not provided	65	220	66	84	62	F	EUR	0	0	0
24	12-lea d	YES	NA	386	6:123366174: G,A	c.1282C>T	p.Arg428 Ter	Pathogenic / Likely pathogenic	Catecholamine Igic	Pathogenic / polymorphic ventricular tachycardia; not provided	56	170	86	114	49	M	EUR	0	0	0
25	12-lea d	YES	NA	387	6:123366174: G,A	c.1282C>T	p.Arg428 Ter	Pathogenic / Likely pathogenic	Catecholamine Igic	Pathogenic / polymorphic ventricular tachycardia; not provided	51	190	96	94	67	M	EUR	0	0	0
26	12-lea d	YES	NA	424	6:123366174: G,A	c.1282C>T	p.Arg428 Ter	Pathogenic / Likely pathogenic	Catecholamine Igic	Pathogenic / polymorphic ventricular tachycardia; not provided	56	152	82	116	70	F	EUR	0	0	0
27	12-lea d	YES	NA	440	6:123366174: G,A	c.1282C>T	p.Arg428 Ter	Pathogenic / Likely pathogenic	Catecholamine Igic	Pathogenic / polymorphic ventricular tachycardia; not provided	73	220	96	78	66	M	EUR	0	0	0
28	12-lea d	YES	NA	411	6:123366174: G,A	c.1282C>T	p.Arg428 Ter	Pathogenic / Likely pathogenic	Catecholamine Igic	Pathogenic / polymorphic ventricular tachycardia; not provided	65	206	86	110	64	F	EUR	0	0	0
29	12-lea d	YES	NA	422	6:123438062: C,T	c.1051+1G> A	NA	Likely pathogenic	Catecholamine Igic	Pathogenic / polymorphic ventricular tachycardia;	54	158	76	124	54	F	EUR	0	0	0
30	12-lea d	YES	NA	389	6:123503899: G,A	c.613C>T	p.Gln205 Ter	Pathogenic	Catecholamine Igic	Ventricular tachycardia; catecholaminergic polymeric, 5, with or without muscle weakness; not provided	56	126	96	102	61	M	EUR	0	0	0

3-1	12-lea-d	YES	NA	376	6:12350389:G,A	c.613C>T	p.Gln205Ter	Pathogenic	Catecholamine ergic polymorphic ventricular tachycardia; ventricular tachycardia, catecholaminer gic polymorphic, 5, with or without muscle weakness; not provided	55	160	68	88	52	F	EUR	0	0	0	0
1	3-lea-d	YES	NA	395	7:150947728:C,T	c.2843G>A	p.Arg948His	Likely pathogenic	Congenital long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome;	67	120	88	76	60	M	EUR	1	0	1	1
2	3-lea-d	YES	NA	451	7:150947795:GC;G	c.2775dupG	p.Pro926Alas	Pathogenic	Cardiovascular phenotype; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome;	81	110	90	82	50	M	EUR	0	0	0	0
3	3-lea-d	YES	NA	484	7:150951555:G,A	c.1838C>T	p.Thr613Met	Pathogenic	Cardiovascular phenotype; Congenital long QT syndrome; Long QT syndrome; Long QT syndrome; not provided	70	116	98	76	53	F	EUR	0	0	0	0
4	3-lea-d	YES	NA	430	7:150951643:C,T	c.1750G>A	p.Gly584Ser	Pathogenic	Cardiovascular phenotype; Congenital long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Romano-Ward Syndrome; Short Q syndrome 1; Q syndrome 1; not provided	61	190	100	122	43	M	EUR	0	0	0	0
5	3-lea-d	YES	NA	414	7:150951649:G,A	c.1744C>T	p.Arg582Cys	Pathogenic	Congenital long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome;	60	158	72	82	50	F	EUR	0	0	0	0
6	3-lea-d	YES	NA	380	7:150955481:G,A	c.1128+1810C>T	NA	Likely pathogenic	Syndrome 2; Short QT syndrome 1; not provided	75	148	84	114	52	M	EUR	0	0	0	0

KCNH2

1	3-lea-d	YES	NA	395	7:150947728:C,T	c.2843G>A	p.Arg948His	Likely pathogenic	Congenital long QT syndrome; Long QT syndrome; Long QT syndrome;	67	120	88	76	60	M	EUR	1	0	1	1
2	3-lea-d	YES	NA	451	7:150947795:GC;G	c.2775dupG	p.Pro926Alas	Pathogenic	Cardiovascular phenotype; Long QT syndrome; Long QT syndrome; Long QT syndrome;	81	110	90	82	50	M	EUR	0	0	0	0
3	3-lea-d	YES	NA	484	7:150951555:G,A	c.1838C>T	p.Thr613Met	Pathogenic	Cardiovascular phenotype; Congenital long QT syndrome; Long QT syndrome; Long QT syndrome;	70	116	98	76	53	F	EUR	0	0	0	0
4	3-lea-d	YES	NA	430	7:150951643:C,T	c.1750G>A	p.Gly584Ser	Pathogenic	Cardiovascular phenotype; Congenital long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome; Long QT syndrome;	61	190	100	122	43	M	EUR	0	0	0	0
5	3-lea-d	YES	NA	414	7:150951649:G,A	c.1744C>T	p.Arg582Cys	Pathogenic	Congenital long QT syndrome; Long QT syndrome; Long QT syndrome;	60	158	72	82	50	F	EUR	0	0	0	0
6	3-lea-d	YES	NA	380	7:150955481:G,A	c.1128+1810C>T	NA	Likely pathogenic	Syndrome 2; Short QT syndrome 1; not provided	75	148	84	114	52	M	EUR	0	0	0	0

7	3-lea d	YES	NA	419	7:150955481: G>A	c.1128+181 0C>T	NA	Likely pathogenic	Long QT syndrome; Short QT syndrome 1; not provided	73	138	72	88	61	F EUR 0 0 0 0
8	3-lea d	YES	NA	448	7:150955481: G,A	c.1128+181 0C>T	NA	Likely pathogenic	Long QT phenotype; Short QT syndrome 1;	67	142	80	116	58	F EUR 0 0 0 0
9	3-lea d	YES	NA	471	7:150957291: C,T	c.1128G>A	p.Gln376 =	Pathogenic / Likely pathogenic	Cardiovascular phenotype; Long QT syndrome; not provided	70	154	82	100	58	F EUR 0 0 0 0
10	3-lea d	YES	NA	468	7:150958059: C,A	c.916G>T	p.Gly306 Trp	Likely pathogenic	Long QT syndrome 2; Short QT syndrome 1; not provided	73	128	84	82	52	F EUR 0 0 0 0
11	12-lea d	YES	NA	438	7:150957291: C,T	c.1128G>A	p.Gln376 =	Pathogenic / Likely pathogenic	Cardiovascular phenotype; Long QT syndrome; not provided	56	148	76	106	64	F EUR 0 0 0 0
1	3-lea d	YES	NA	454	11:2570637:C T,C	c.488delT	p.Leu163 Argfs	Pathogenic	Cardiovascular phenotype; Congenital long QT syndrome; Long QT syndrome; Long QT syndrome 1; not provided	64	146	72	120	54	F EUR 1 0 0 0
2	3-lea d	YES	NA	446	11:2570652: G,A	c.502G>A	p.Gly168 Arg	Pathogenic	Cardiovascular phenotype; Congenital long QT syndrome; Long QT syndrome; Long QT syndrome 1; not provided	60	124	92	102	61	M EUR 0 0 0 0
3	3-lea d	YES	NA	437	11:2570664: GTGGTCCG CCTC:G	c.524_534d del1	p.Leu175 Argfs	Pathogenic	Cardiovascular phenotype	62	152	70	88	59	F EUR 0 0 0 0
4	3-lea d	YES	NA	490	11:2570719: GGCTGC:G	c.573_577d elGCCTGCT	p.Arg192 Cysfs	Pathogenic	Cardiovascular phenotype; Jervell and Lange-Nielsen syndrome; Jervell and Lange-Nielsen syndrome 1; Long QT syndrome; not provided	71	160	94	108	46	F EUR 0 0 0 0
5	3-lea d	YES	NA	472	11:2570719: elGCCTGCT	c.573_577d p.Arg192 Cysts	Pathogenic	Cardiovascular phenotype; Jervell and Lange-Nielsen syndrome; Jervell and Lange-Nielsen syndrome 1; Long QT	75	130	88	98	50	M EUR 0 0 0 0	

KCNQ1

Syndrome; not provided														
6	3-lead	YES	NA	424	11:2570742A: :G	c.592A>G	p.Ile198V al	Pathogenic	Congenital long QT syndrome; not provided	73	148	90	108	M
7	3-lead	YES	NA	421	11:2571391C: :T	c.671C>T	p.Thr224 Met	Likely pathogenic	Congenital long QT syndrome; Long QT syndrome	64	152	90	88	M
8	3-lead	YES	NA	504	11:2572862:T: :C	c.797T>C	p.Leu266 Pro	Pathogenic	Cardiovascular phenotype: Congenital long QT syndrome; Long QT syndrome; not provided	72	136	90	108	M
9	3-lead	YES	NA	454	11:2572870: :G,A	c.805G>A	p.Gly269 Ser	Pathogenic	Atrial fibrillation, familial; 3; Beckwith- Wiedemann syndrome; Congenital long QT syndrome; Jervell and Lange-Nielsen Syndrome 1; Long QT syndrome; Long QT syndrome 1; Long QT syndrome 1; Short QT syndrome 2; Syndrome 2; not provided	67	116	86	92	M
10	3-lead	YES	NA	424	11:2572870: :G,A	c.805G>A	p.Gly269 Ser	Pathogenic	Atrial fibrillation, familial; 3; Beckwith- Wiedemann syndrome; Congenital long QT syndrome; Jervell and Lange-Nielsen Syndrome 1; Long QT syndrome; Long QT syndrome 1; Long QT syndrome 1; Short QT syndrome 2; Syndrome 2; not provided	60	174	88	98	M
11	3-lead	YES	NA	519	11:2583519: :GC,G	c.1008delC	p.Ile337S ufs	Pathogenic	not provided	58	184	100	94	F

microcephaly;
Short QT
syndrome 2;
Toe
clinodactyly;
not provided

Anomaly of
the cerebral
white matter;
Anomaly of
the nares;
Atrial
fibrillation,
familial, 3;
Beckwith-
Wiedemann
syndrome;
Congenital
long QT
syndrome;
Congenital
microcephaly;
Decreased
fetal
movement;
Diffuse white
matter
abnormalities;
Enlarged naris;
Generalized
hypotonia;
Generalized
neonatal
hypotonia;
High palate;
Jervell and
Lange-Nielsen
Syndrome 1;
Long QT
syndrome;
Long QT
syndrome 1;
Neonatal
hypotonia;
Polyhydramnio
s; Postnatal
microcephaly;
Short QT
syndrome 2;
Toe
clinodactyly;
not provided

15	3- lea d	YES	NA	451	11:2585264:A :G	c.1085A>G	p.Lys362 Arg	Pathogenic	66	142	68	114	52	F	EUR	0	0	0	0	
16	3- lea d	YES	NA	390	11:2587631: G.A	c.1190G>A	p.Arg397 Gln	Likely pathogenic	not provided	73	130	86	84	47	M	EUR	0	0	0	0
17	3- lea d	YES	NA	398	11:2587631: G.A	c.1190G>A	p.Arg397 Gln	Likely pathogenic	not provided	55	134	84	96	55	M	EUR	0	0	0	0
18	3- lea d	YES	NA	419	11:2587631: G.A	c.1190G>A	p.Arg397 Gln	Likely pathogenic	not provided	88	112	100	66	49	M	EUR	0	0	0	0

19	3-lea ^d	YES	NA	500	11:2661960: G>T	c.1394- 1G>T	NA	Pathogenic	Cardiovascular phenotype; Long QT syndrome; not provided	59	154	88	122	57	F	EUR	0	0	0	0	
20	3-lea ^d	YES	NA	475	11:2661960: G>T	c.1394- 1G>T	NA	Pathogenic	Cardiovascular phenotype; Long QT syndrome; not provided	83	152	78	92	56	F	EUR	0	0	0	0	
21	3-lea ^d	YES	NA	424	11:2661960: G>T	c.1394- 1G>T	NA	Pathogenic	Cardiovascular phenotype; Long QT syndrome; not provided	84	136	90	76	58	M	EUR	0	0	0	0	
22	12-lea ^d	YES	NA	457	11:2583535:C >A	c.1022C>A	p.Ala341 Glu	Pathogenic	Abnormality of the cerebral white matter; Abnormality of the nerves; Arrtrial fibrillation, familial, 3; Beckwith- Wiedemann syndrome; Congenital long QT syndrome; Congenital microcephaly; Decreased fetal movement; Diffuse white matter	Cardiovascular phenotype; Congenital long QT syndrome; Long QT syndrome 1; Long QT syndrome 12; digenic; not provided	51	158	94	78	71	M	EUR	0	0	0	0
23	12-lea ^d	YES	NA	441	11:2585264:A >G	c.1085A>G	p.Lys362 Arg	Pathogenic / Likely pathoge nic	Enlarged nans; Generalized hypotonia; Generalized neonatal hypotonia; High palate; Jervell and Lange-Nielsen syndrome 1; Long QT syndrome; Long QT syndrome 1; Neonatal hypotonia;	67	178	84	74	72	M	EUR	0	0	0	0	

Polyhydramnios;
Postnatal microcephaly;
Short QT syndrome;
Syndrome 2;
Toe clinodactyly;
not provided

24	12-lead	YES	NA	429	11:2587631: G,A	c.1190G>A	p.Arg397Gln	Likely pathogenic	not provided	70	180	84	76	69	F	EUR	0	0	0
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25	12-lead	YES	NA	435	11:2570719: GGCTGC:G	c.573_577d el	p.Arg192Cysfs	Pathogenic	Cardiovascular phenotype; Jervell and Lange-Nielsen syndrome; Lange-Nielsen syndrome 1; Long QT syndrome; not provided	63	176	88	108	68	F	EUR	0	0	0
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provided

26	12-lead	YES	NA	455	11:2661960: G,T	c.1394-1G>T	NA	Pathogenic / Likely pathogenic	Cardiovascular phenotype; Long QT syndrome; not provided	59	130	94	98	60	M	EUR	0	0	0
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provided

		KCNJ2	1	3-lead	YES	NA	483	12:2566465:C :T	c.1552G>T	p.Arg518Cys	Pathogenic	Long QT syndrome; not provided	113	150	92	72	M	EUR	1	1	0
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provided

		SNTA1	1	3-lead	YES	NA	390	20:33410203: G,A	c.1169G>T	p.Ala390Val	Likely pathogenic	Long QT syndrome 12; not provided	64	114	96	94	F	EUR	0	0	0
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provided

		KCNE2	1	3-lead	YES	NA	405	21:34370825: C:T	c.347C>T	p.Ala116Val	Likely pathogenic	Acquired long QT syndrome; not provided	66	112	70	80	M	EUR	0	0	0
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provided

		KCNE2	2	3-lead	YES	NA	431	21:34370840: T:A	c.362T>A	p.Met121Lys	Likely pathogenic	not provided	67	134	84	84	M	EUR	1	0	0
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provided

		KCNE2	3	12-lead	YES	NA	423	21:34370840: T,A	c.362T>A	p.Met121Lys	Likely pathogenic	not provided	50	114	92	78	M	EUR	0	0	0
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provided

Note: Variants are restricted to the canonical transcript (ENST00000337385.7, KCNE1); Lead , # lead in electrocardiogram; cDNA, cDNA consequence; protein, protein consequence; Csq, consequence; QC, quality control; PR, PR-interval duration; HR, heart rate; QRS, QRS-complex duration; QTc, Bazett correct QT-interval duration; PWD, P-wave duration; Anc, ancestry; BB, beta blocker usage; CCB, calcium channel blocker usage

Supplemental Table XIV. Proportion of carriers of LOF or pathogenic variants with 1st degree AV Block or QTc prolongation

Phenotype	Gene set	TOPMed 12-lead			UK Biobank 3-lead			UK Biobank 12-lead			MyCode*			Total		
		Carrier	Case	Percent	Carrier	Case	Percent	Carrier	Case	Percent	Carrier	Case	Percent			
1st degree AV Block (PR ≥ 200 ms)	SCN5A	9	3	33.33	10	1	10.00	8	3	37.50	43	17	39.53	70	24.00	34.29
	Likely pathogenic and pathogenic variants	21	5	23.81	12	0	0.00	11	3	27.27	73	25	34.25	117	33.00	28.21
	SCN5A	28	6	21.43	14	1	7.14	12	4	33.33	89	30	33.71	143	41.00	28.67
	Loss-of-function variants															
	KCNQ1	16	4	25.00	9	3	33.33	2	0	0.00	51	16	31.37	78	23.00	29.49
	KCNH2	5	2	40.00	4	0	0.00	2	0	0.00	10	4	40.00	21	6.00	28.57
	SCN5A	9	0	0.00	8	1	12.50	7	0	0.00	40	3	7.50	64	4.00	6.25
	KCNQ1, KCNH2	21	6	28.57	13	3	23.08	4	0	0.00	61	20	32.79	99	29.00	29.29
	KCNQ1, KCNH2, SCN5A	30	6	20.00	21	4	19.05	11	0	0.00	101	23	22.77	163	33.00	20.25
	Likely pathogenic and pathogenic variants															
	KCNQ1	52	7	13.46	21	4	19.05	5	0	0.00	133	35	26.32	211	46.00	21.80
	KCNH2	11	3	27.27	10	1	10.00	1	0	0.00	33	6	18.18	55	10.00	18.18
	SCN5A	19	2	10.53	10	0	0.00	11	0	0.00	71.00	6.00	8.45	111	8.00	7.21
	QTc prolongation (QTc interval ≥ 480ms)															
	KCNQ1, KCNH2, SCN5A	63	10	15.87	31	5	16.13	6	0	0.00	166.00	41.00	24.70	266	56.00	21.05
	Loss-of-function and likely pathogenic and pathogenic variants															
	KCNQ1	55	7	12.73	22	4	18.18	5	0	0.00	142	35	24.65	224	46.00	20.54
	KCNH2	12	3	25.00	13	1	7.69	3	0	0.00	39	9	23.08	67	13.00	19.40
	SCN5A	26	2	7.69	12	1	8.33	11	0	0.00	87.00	8.00	9.20	136	11.00	8.09
	KCNQ1, KCNH2	67	10	14.93	35	5	14.29	8	0	0.00	181.00	44.00	24.30	291	59.00	20.27
	KCNQ1, KCNH2, SCN5A	93	12	12.90	47	6	12.77	19	0	0.00	268	52	19.40	427	70.00	16.39
	Loss-of-function variants															
	KCNQ1	16	3	18.75	9	4	44.44	2	0	0.00	51	20	39.22	78	27.00	34.62
	KCNH2	5	2	40.00	4	0	0.00	2	0	0.00	10	6	60.00	144	8.00	5.56
	SCN5A	9	0	0.00	8	1	12.50	7	0	0.00	40	3	7.50	64	4.00	6.25
	KCNQ1, KCNH2	21	5	23.81	13	4	30.77	4	0	0.00	61	26	42.62	99	35.00	35.35
	KCNQ1, KCNH2, SCN5A	30	5	16.67	21	5	23.81	11	0	0.00	101	29	28.71	163	39.00	23.93
	Likely pathogenic and pathogenic variants															
	KCNQ1	52	6	11.54	21	5	23.81	5	0	0.00	133	41	30.83	211	52.00	24.64
	KCNH2	11	2	18.18	10	1	10.00	1	0	0.00	33	10	30.30	55	13.00	23.64
	SCN5A	19	2	10.53	10	0	0.00	11	1	9.09	71.00	8.00	10.96	111	11.00	9.91
	KCNQ1, KCNH2	63	8	12.70	31	6	19.35	6	0	0.00	166.00	51.00	30.72	266	65.00	24.44
	KCNQ1, KCNH2, SCN5A	82	10	12.20	41	6	14.63	17	1	5.88	237.00	59.00	24.89	377	76.00	20.16
	Loss-of-function and likely pathogenic and pathogenic variants															
	KCNQ1	55	6	10.91	22	5	22.73	5	0	0.00	142	41	28.87	224	52.00	23.21
	KCNH2	12	2	16.67	13	1	7.69	3	0	0.00	39	13	33.33	67	16.00	23.88

	SCN5A	26	2	7.69	12	1	8.33	11	1	9.09	87.00	10.00	11.49	136	14.00	10.29
KCNQ1,																
KCNH2		67	8	11.94	35	6	17.14	8	0	0.00	181.00	54.00	29.83	291	68.00	23.37
KCNQ1,																
KCNH2,																
SCN5A		93	10	10.75	47	7	14.89	19	1	5.26	268	64	23.88	427	82.00	19.20

Note, First degree AV block (PR interval > 200), QT prolongation (QTc interval \geq 480), Sex-stratified QTc prolongation based on 99 percentile (male: QTc interval \geq 468.1162, female: QTc interval \geq 482.452) based on distribution in UK Biobank

Supplemental Table XV. Logistic firth's regression results for LOF and likely pathogenic and pathogenic variants in KCNQ1, KCNH2 and SCN5A for PR and QTc prolongation in TOPMed, UK Biobank and MyCode

Individual cohort results

Phenotype	Gene	OR	95%CI	P value	N	Carrier Percent	N	Carrier Percent	OR	95% CI	TOPMed			UK Biobank (3-head)					
											Case	Control	Case	Control					
Loss-of-function variants																			
	<i>SCN5A</i>	11.93	[1.47, 96.68]	2.02E-02	1721	2	0.12	16977	2	0.01	6.53	[1.01, 42.19]	4.88E-02	489	1	0.2	20968	9	0.04
1st degree AV block (PR ≥ 200 ms)	<i>SCN5A</i>	4.44	[0.84, 23.33]	7.83E-02	1721	2	0.12	16977	7	0.04	1.46	[0.07, 29.14]	8.06E-01	489	0	0	20968	12	0.06
	<i>SCN5A</i>	3.65	[0.76, 17.58]	1.06E-01	1721	2	0.12	16977	9	0.05	4.4	[0.73, 26.44]	1.05E-01	489	1	0.2	20968	13	0.06
Loss-of-function variants																			
	<i>KCNQ1</i>	11.19	[3.72, 33.64]	1.71E-05	1424	6	0.42	20353	8	0.04	11.19	[3.72, 33.64]	1.71E-05	1424	6	0.42	20353	8	0.04
	<i>KCNH2</i>	13.59	[1.29, 143.66]	3.01E-02	1424	1	0.07	20353	2	0.01	13.59	[1.29, 143.66]	3.01E-02	1424	1	0.07	20353	2	0.01
	<i>SCN5A</i>	1.2	[0.05, 27.62]	9.10E-01	1424	0	0	20353	6	0.03	1.2	[0.05, 27.62]	9.10E-01	1424	0	0	20353	6	0.03
QTc ≥ 460ms	<i>KCNQ1</i>	11.29	[4.14, 30.77]	2.17E-06	1424	7	0.49	20353	10	0.05	11.29	[4.14, 30.77]	2.17E-06	1424	7	0.49	20353	10	0.05
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	7.07	[2.84, 17.61]	2.64E-05	1424	7	0.49	20353	16	0.08	7.07	[2.84, 17.61]	2.64E-05	1424	7	0.49	20353	16	0.08
Likely pathogenic and pathogenic variants																			
	<i>KCNQ1</i>	10.95	[5.05, 23.76]	1.39E-09	1424	12	0.84	20353	18	0.09	10.95	[5.05, 23.76]	1.39E-09	1424	12	0.84	20353	18	0.09
	<i>KCNH2</i>	14.49	[3.67, 57.12]	1.34E-04	1424	4	0.28	20353	5	0.02	14.49	[3.67, 57.12]	1.34E-04	1424	4	0.28	20353	5	0.02
	<i>SCN5A</i>	7.37	[1.95, 27.81]	3.21E-03	1424	3	0.21	20353	8	0.04	7.37	[1.95, 27.81]	3.21E-03	1424	3	0.21	20353	8	0.04
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	11.67	[5.94, 22.94]	1.00E-12	1424	16	1.12	20353	23	0.11	11.67	[5.94, 22.94]	1.00E-12	1424	16	1.12	20353	23	0.11
Loss-of-function and likely pathogenic and pathogenic variants	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	10.45	[5.73, 19.04]	1.79E-14	1424	19	1.33	20353	31	0.15	10.45	[5.73, 19.04]	1.79E-14	1424	19	1.33	20353	31	0.15
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	8.77	[4.98, 15.44]	5.77E-14	1424	20	1.4	20353	38	0.19	8.77	[4.98, 15.44]	5.77E-14	1424	20	1.4	20353	38	0.19
Loss-of-function variants																			
	<i>KCNQ1</i>	28.51	[8.42, 96.46]	7.19E-08	367	4	1.09	21410	10	0.05	70.55	[16.85, 295.38]	5.67E-09	134	3	2.24	19346	6	0.03
	<i>KCNH2</i>	69.69	[6.39, 760.42]	5.00E-04	367	1	0.27	21410	2	0.01	20.71	[32.7, 576.17]	7.41E-02	134	0	0	19346	4	0.02
	<i>SCN5A</i>	4.71	[0.2, 112.25]	3.38E-01	367	0	0	21410	6	0.03	24.13	[3.62, 160.82]	1.00E-03	134	1	0.75	19346	7	0.04
	<i>KCNQ1</i> , <i>KCNH2</i>	32.55	[10.83, 97.81]	5.47E-10	367	5	1.36	21410	12	0.06	48.43	[13.14, 178.46]	5.50E-09	134	3	2.24	19346	10	0.05

	<i>KCNQ1</i> , <i>KCNH2</i>	23.14	[10.2 52.49]	5.49E- 14	466	9	193	19014	18	0.09
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	16.46	[7.87 34.41]	9.63E- 14	466	10	2.15	19014	27	0.14
Loss-of-function and likely pathogenic and pathogenic variants										
	<i>KCNQ1</i>	24.31	[8.96, 65.95]	3.69E- 10	466	6	1.29	19014	12	0.06
	<i>KCNH2</i>	13.36	[3.71, 48.16]	7.42E- 05	466	3	0.64	19014	10	0.05
	<i>SCN5A</i>	9.44	[2.21, 40.23]	2.41E- 03	466	2	0.43	19014	10	0.05
	<i>KCNQ1</i> , <i>KCNH2</i>	18.65	[8.46 41.14]	4.18E- 13	466	9	1.93	19014	22	0.12
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	15.24	[7.6, 30.57]	1.76E- 14	466	11	2.36	19014	32	0.17
Loss-of-function variants										
	<i>KCNQ1</i>	14.07	[0.28, 707.11]	1.86E- 01	91	0	0	6776	2	0.03
	<i>KCNH2</i>	25.51	[0.59, 1109.15]	9.24E- 02	91	0	0	6776	2	0.03
	<i>SCN5A</i>	5.02	[0.24, 105.52]	3.00E- 01	91	0	0	6776	7	0.1
	<i>KCNQ1</i> , <i>KCNH2</i>	10.22	[0.35, 296.69]	1.76E- 01	91	0	0	6776	4	0.06
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	3.55	[0.19, 66.88]	3.98E- 01	91	0	0	6776	11	0.16
Likely pathogenic and pathogenic variants										
	<i>KCNQ1</i>	7.66	[0.31, 187.03]	2.12E- 01	91	0	0	6776	5	0.07
	<i>KCNH2</i>	14.72	[0.15, 1475.92]	2.53E- 01	91	0	0	6776	1	0.01
	<i>SCN5A</i>	3.03	[0.16, 58.24]	4.62E- 01	91	0	0	6776	11	0.16
	<i>KCNQ1</i> , <i>KCNH2</i>	5.69	[0.25, 129.86]	2.76E- 01	91	0	0	6776	6	0.09
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	2.06	[0.12, 35.86]	6.19E- 01	91	0	0	6776	17	0.25
Loss-of-function and likely pathogenic and pathogenic variants										
	<i>KCNQ1</i>	7.66	[0.31, 187.03]	2.12E- 01	91	0	0	6776	5	0.07
	<i>KCNH2</i>	11.33	[0.33, 390.57]	1.79E- 01	91	0	0	6776	3	0.04
	<i>SCN5A</i>	3.03	[0.16, 58.24]	4.62E- 01	91	0	0	6776	11	0.16
	<i>KCNQ1</i> , <i>KCNH2</i>	4.91	[0.24, 101.65]	3.03E- 01	91	0	0	6776	8	0.12
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	1.94	[0.11, 33.34]	6.46E- 01	91	0	0	6776	19	0.28
Loss-of-function variants										
	<i>KCNQ1</i>	50.44	[7.23 351.65]	7.58E- 05	57	1	1.75	19423	8	0.04
	<i>KCNH2</i>	50.72	[1.88, 1370.47]	1.96E- 02	57	0	0	19423	4	0.02
	<i>SCN5A</i>	15.76	[0.73, 339.11]	7.82E- 02	57	0	0	19423	8	0.04
	<i>KCNQ1</i> , <i>KCNH2</i>	38.8	[6.26, 240.36]	8.44E- 05	57	1	1.75	19423	12	0.06
	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>	22.2	[4, 123.16]	3.91E- 04	57	1	1.75	19423	20	0.1

Likely pathogenic and pathogenic variants									
KCNQ1	55.89	[13.4, 233.12]	3.36E- 08	57	2	3.51	19423	15	0.08
KCNH2	16.2	[0.92, 284.85]	5.69E- 02	57	0	0	19423	10	0.05
SCN5A	16.97	[0.89, 323.81]	5.98E- 02	57	0	0	19423	10	0.05
KCNQ1'	34.25	[9.03, 129.91]	2.04E- 07	57	2	3.51	19423	25	0.13
KCNQ1', KCNH2,	24.98	[6.85, 91.08]	1.09E- 06	57	2	3.51	19423	35	0.18
Loss-of-function and likely pathogenic and pathogenic variants									
KCNQ1	51.83	[12.57, 213.65]	4.67E- 08	57	2	3.51	19423	16	0.08
KCNH2	13.37	[0.88, 223.27]	7.11E- 02	57	0	0	19423	13	0.07
SCN5A	12.23	[0.65, 231.15]	9.50E- 02	57	0	0	19423	12	0.06
KCNQ1', KCNH2,	30.12	[8.07, 112.48]	4.07E- 07	57	2	3.51	19423	29	0.15
KCNQ1', KCNH2,	20.81	[5.77, 75.11]	3.55E- 06	57	2	3.51	19423	41	0.21
Loss-of-function variants									
KCNQ1	13.31	[0.29, 615.6]	1.86E- 01	101	0	0	6766	2	0.03
KCNH2	16.86	[0.38, 739.34]	1.43E- 01	101	0	0	6766	2	0.03
SCN5A	4.8	[0.23,	3.15E- 01	101	0	0	6766	7	0.1
KCNQ1', KCNH2	8.37	[0.31, 229.21]	2.08E- 01	101	0	0	6766	4	0.06
KCNQ1', KCNH2,	3.22	[0.17, 60.65]	4.35E- 01	101	0	0	6766	11	0.16
SCN5A									
Likely pathogenic and pathogenic variants									
KCNQ1	6.09	[0.26, 144.26]	2.63E- 01	101	0	0	6766	5	0.07
KCNH2	14.54	[0.15, 1443.33]	2.54E- 01	101	0	0	6766	1	0.01
SCN5A	10.24	[1.67, 62.86]	1.20E- 02	101	1	0.99	6766	10	0.15
KCNQ1', KCNH2	4.78	[0.22, 105.83]	3.22E- 01	101	0	0	6766	6	0.09
KCNQ1', KCNH2,	6.24	[1.12, 34.94]	3.71E- 02	101	1	0.99	6766	16	0.24
Loss-of-function and likely pathogenic and pathogenic variants									
KCNQ1	6.09	[0.26, 144.26]	2.63E- 01	101	0	0	6766	5	0.07
KCNH2	9.34	[0.29, 300.93]	2.07E- 01	101	0	0	6766	3	0.04
SCN5A	10.24	[1.67, 62.86]	1.20E- 02	101	1	0.99	6766	10	0.15
KCNQ1', KCNH2,	3.95	[0.2, 79.78]	3.70E- 01	101	0	0	6766	8	0.12
SCN5A	5.7	[1.03, 31.43]	4.56E- 02	101	1	0.99	6766	18	0.27

Meta-analysis results

Meta-analysis results												
	Inverse variance fixed effects			Random effects (Prause-Mander estimator)			Case					
	OR	95% CI	P value	OR	95% CI	P value	N	Carrier	Percent	N	Carrier	Percent
Loss-of-function variants												
SCN5A	8.72	[3.17, 24]	2.75E-05	8.72	[3.17, 24]	2.75E-05	2782	6	0.22	44362	16	0.04
1st degree AV block (PR ≥ 200 ms)												
Likely pathogenic and pathogenic variants	4.8	[1.79, 12.9]	1.84E-03	4.8	[1.79, 12.9]	0.00184426	2782	5	0.18	44362	27	0.06
SCN5A	5.55	[2.36, 13.03]	8.44E-05	5.55	[2.36, 13.03]	8.44E-05	2782	7	0.25	44362	30	0.07
Loss-of-function variants												
KCNQ1	16.29	[8.31, 31.92]	4.35E-16	17.15	[6.76, 43.53]	2.22E-09	3314	17	0.51	59720	20	0.03
KCNH2	10.94	[2.46, 48.63]	1.68E-03	10.94	[2.46, 48.63]	0.002	3314	2	0.06	59720	8	0.01
SCN5A	6.66	[1.85, 24.02]	3.74E-03	4.65	[0.78, 27.63]	0.1	3314	2	0.06	59720	18	0.03
KCNQ1, KCNH2, SCN5A	14.38	[7.88, 26.24]	3.84E-18	14.38	[7.88, 26.24]	3.84E-18	3314	19	0.57	59720	28	0.05
Likely pathogenic and pathogenic variants												
KCNQ1	13.41	[8.28, 21.71]	4.83E-26	13.59	[7.99, 23.12]	6.27E-22	3314	30	0.91	59720	47	0.08
KCNH2	15.84	[7.19, 34.9]	7.18E-12	15.84	[7.19, 34.9]	7.18E-12	3314	11	0.33	59720	17	0.03
SCN5A	7.06	[3.06, 16.26]	4.45E-06	7.06	[3.06, 16.26]	4.45E-06	3314	7	0.21	59720	25	0.04
QTc ≥ 460ms												
KCNQ1, KCNH2, SCN5A	13.89	[9.19, 20.98]	7.58E-36	13.89	[9.19, 20.99]	8.54E-36	3314	41	1.24	59720	64	0.11
KCNQ1, KCNH2, SCN5A	11.7	[8.1, 16.9]	2.94E-39	11.7	[8.1, 16.9]	2.94E-39	3314	48	1.45	59720	89	0.15
Loss-of-function and likely pathogenic and pathogenic variants												
KCNQ1	12.51	[7.87, 19.87]	1.09E-26	12.61	[7.72, 20.57]	3.65E-24	3314	32	0.97	59720	52	0.09
KCNH2	12.55	[5.92, 26.59]	4.14E-11	12.55	[5.92, 26.59]	4.14E-11	3314	11	0.33	59720	22	0.04
SCN5A	5.79	[2.72, 12.28]	4.89E-06	5.79	[2.72, 12.28]	4.89E-06	3314	8	0.24	59720	34	0.06
KCNQ1, KCNH2	12.34	[8.31, 18.33]	1.27E-35	12.34	[8.31, 18.33]	1.27E-35	3314	43	1.3	59720	74	0.12
KCNQ1, KCNH2, SCN5A	10.06	[7.11, 14.23]	7.94E-39	10.06	[7.11, 14.23]	7.94E-39	3314	51	1.54	59720	108	0.18
Loss-of-function variants												
KCNQ1	39.38	[15.96, 97.16]	1.58E-15	39.38	[15.96, 97.16]	1.58E-15	592	7	1.18	47532	18	0.04
KCNH2	40.73	[7.25, 28.77]	2.55E-05	40.73	[7.25, 228.77]	2.55E-05	592	1	0.17	47532	8	0.02
SCN5A	12.18	[2.9, 51.18]	6.45E-04	12.18	[2.9, 51.18]	6.45E-04	592	1	0.17	47532	20	0.04
KCNQ1, KCNH2	35.53	[15.71, 80.34]	9.71E-18	35.53	[15.71, 80.34]	9.71E-18	592	8	1.35	47532	26	0.05
KCNQ1, KCNH2, SCN5A	23.51	[11.39, 48.52]	1.35E-17	23.02	[10.29, 51.46]	2.18E-14	592	9	1.52	47532	46	0.01
Likely pathogenic and pathogenic variants												
KCNQ1	30.42	[15.26, 60.64]	2.93E-22	30.47	[14.89, 62.36]	8.60E-21	592	11	1.86	47532	41	0.09
KCNH2	22.89	[7.23, 72.43]	1.00E-07	22.89	[7.23, 72.43]	1.00E-07	592	3	0.51	47532	17	0.04
SCN5A	6.89	[1.74, 27.24]	5.93E-03	6.89	[1.74, 27.24]	5.93E-03	592	1	0.17	47532	31	0.07
QTc ≥ 480ms												
KCNQ1, KCNH2, SCN5A	26.67	[14.6, 48.74]	1.30E-26	26.67	[14.6, 48.74]	1.30E-26	592	14	2.36	47532	58	0.12
KCNQ1, KCNH2, SCN5A	19.32	[11.01, 33.88]	5.14E-25	16.82	[5.97, 47.41]	9.28E-08	592	15	2.53	47532	89	0.19
Loss-of-function and likely pathogenic and pathogenic variants												
KCNQ1	26.36	[13.37, 51.99]	3.56E-21	26.5	[12.79, 54.9]	1.19E-18	592	11	1.86	47532	45	0.09
KCNH2	19.08	[6.34, 57.39]	1.54E-07	19.08	[6.34, 57.39]	1.54E-07	592	3	0.51	47532	23	0.05
SCN5A	8.82	[2.77, 28.04]	2.26E-04	8.82	[2.77, 28.04]	2.26E-04	592	2	0.34	47532	36	0.08
KCNQ1, KCNH2	22.66	[12.54, 40.93]	4.47E-25	22.66	[12.54, 40.93]	4.47E-25	592	14	2.36	47532	68	0.14

KCNQ1, KCNH2, SCN5A	17.45	[10.19, 29.88]	2.07E-25	15.02	[5.02, 44.9]	1.25E-06	592	16	2.7	47532	104	0.22
Loss-of-function variants												
KCNQ1	35.13	[11.78, 104.72]	1.71E-10	35.13	[11.78, 104.72]	1.71E-10	225	3	1.33	62809	34	0.05
KCNH2	205.62	[45.54, 928.45]	4.37E-12	205.62	[45.54, 928.45]	4.37E-12	225	2	0.89	62809	8	0.01
SCN5A	16.57	[2.64, 103.82]	2.72E-03	16.57	[2.64, 103.82]	0.003	225	0	0	62809	20	0.03
KCNQ1, KCNH2	48.96	[19.66, 121.94]	6.37E-17	48.96	[19.66, 121.94]	6.37E-17	225	5	2.22	62809	42	0.07
KCNQ1, KCNH2, SCN5A	30.63	[12.87, 72.9]	1.04E-14	30.63	[12.87, 72.9]	1.04E-14	225	5	2.22	62809	62	0.1
Likely pathogenic and pathogenic variants												
KCNQ1	30.7	[13.67, 69.21]	1.52E-16	30.7	[13.61, 69.21]	1.52E-16	225	6	2.67	62809	71	0.11
KCNH2	48.56	[14.69, 160.48]	1.93E-10	48.56	[14.69, 160.48]	1.93E-10	225	2	0.89	62809	26	0.04
SCN5A	40.18	[12.36, 130.59]	8.15E-10	40.18	[12.36, 130.59]	8.15E-10	225	2	0.89	62809	30	0.05
KCNQ1, KCNH2	29.58	[14.61, 59.87]	4.72E-21	29.58	[14.61, 59.87]	4.72E-21	225	8	3.56	62809	97	0.15
KCNQ1, KCNH2, SCN5A	28.54	[15.13, 53.83]	4.01E-25	28.54	[15.13, 53.83]	4.01E-25	225	10	4.44	62809	127	0.2
Loss-of-function and likely pathogenic and pathogenic variants												
KCNQ1	27.72	[12.42, 61.85]	4.90E-16	27.72	[12.42, 61.85]	4.90E-16	225	6	2.67	62809	78	0.12
KCNH2	44.01	[13.56, 142.79]	2.93E-10	44.01	[13.56, 142.79]	2.93E-10	225	2	0.89	62809	31	0.05
SCN5A	25.73	[8.14, 81.31]	3.18E-08	25.73	[8.14, 81.31]	3.18E-08	225	2	0.89	62809	40	0.06
KCNQ1, KCNH2	26.46	[13.18, 53.13]	3.27E-20	26.46	[13.18, 53.13]	3.27E-20	225	8	3.56	62809	109	0.17
KCNQ1, KCNH2, SCN5A	23.54	[12.6, 43.99]	4.14E-23	23.54	[12.6, 43.99]	4.14E-23	225	10	4.44	62809	149	0.24
Loss-of-function variants												
KCNQ1	37.49	[14.76, 95.21]	2.53E-14	35.34	[8.53, 146.38]	8.82E-07	675	7	1.04	47449	18	0.04
KCNH2	27.44	[4.85, 155.35]	1.81E-04	27.44	[4.85, 155.35]	1.81E-04	675	1	0.15	47449	8	0.02
SCN5A	10.97	[2.61, 46.04]	1.07E-03	10.97	[2.61, 46.04]	1.07E-03	675	1	0.15	47449	20	0.04
KCNQ1, KCNH2	30.82	[13.58, 69.94]	2.40E-16	29.75	[10.81, 81.89]	5.14E-11	675	8	1.19	47449	26	0.05
KCNQ1, KCNH2, SCN5A	20.9	[10.1, 43.28]	2.68E-16	17.12	[4.91, 59.7]	8.28E-06	675	9	1.33	47449	46	0.1
Likely pathogenic and pathogenic variants												
KCNQ1	25.99	[12.75, 52.98]	3.12E-19	24.43	[8.33, 71.95]	6.16E-09	675	10	1.48	47449	42	0.09
KCNH2	15.59	[4.44, 54.79]	1.84E-05	15.59	[4.44, 54.79]	1.84E-05	675	2	0.3	47449	18	0.04
SCN5A	9.29	[2.85, 30.27]	2.19E-04	9.29	[2.85, 30.27]	2.19E-04	675	2	0.3	47449	30	0.06
KCNQ1, KCNH2	21.34	[11.36, 40.05]	1.68E-21	20.16	[8.03, 50.63]	1.61E-10	675	12	1.78	47449	60	0.13
KCNQ1, KCNH2, SCN5A	15.59	[8.86, 27.45]	1.73E-21	15.08	[7.41, 30.71]	7.35E-14	675	14	2.07	47449	90	0.19
Loss-of-function and likely pathogenic and pathogenic variants												
KCNQ1	22.45	[11.11, 45.39]	4.58E-18	21.18	[6.97, 64.38]	7.34E-08	675	10	1.48	47449	46	0.1
KCNH2	12.77	[3.85, 42.37]	3.12E-05	12.77	[3.85, 42.37]	3.12E-05	675	2	0.3	47449	24	0.05
SCN5A	10.08	[3.57, 28.4]	1.25E-05	10.08	[3.57, 28.4]	1.25E-05	675	3	0.44	47449	35	0.07
KCNQ1, KCNH2	17.96	[9.66, 33.38]	6.72E-20	16.74	[6.54, 42.83]	4.16E-09	675	12	1.78	47449	70	0.15
KCNQ1, KCNH2, SCN5A	14.15	[8.21, 24.39]	1.53E-21	13.1	[5.67, 30.25]	1.69E-09	675	15	2.22	47449	105	0.22

Supplemental Table XVI. Results from collapsed tests for SCN5A LOF variants for all 5 ECG traits

Individual cohort results												TOPMed				3-lead UK Biobank				12-lead UK Biobank				MyCode			
Gene	Group	ECG	Carrier	beta	95% CI	P value	Carrier	beta	95% CI	P value	Carrier	beta	95% CI	P value	Carrier	beta	95% CI	P value									
<i>SCN5A</i>	LOF	RR	9	118.0	[18.87, 217.18]	2.00E-02	11	38.67	[40.06, 117.39]	0.34	8	-20.14	[-128.22, 87.94]	0.71	46	-6.7	[-49.82, 36.42]	0.76									
		PR	9	20.88	[3.73, 8.03]	0.017	10	20.52	[6.54, 34.5]	4.00E-03	8	25.75	[8.19, 43.31]	4.04E-03	43	50.94	[42.71, 59.17]	2.90E-33									
	LOF	PWD	8	9.72	[0.67, 18.77]	3.50E-02	-	-	-	-	8	0.32	[-10.82, 11.46]	0.96	42	20.1	[15.2, 25]	1.50E-15									
		QRS	9	10.65	[2.70, 18.59]	8.60E-03	-	-	-	-	8	5.31	[-2.76, 13.38]	0.2	43	17.8	[13.49, 22.11]	2.00E-15									
LOF	QTc	9	5.45	[-10.04, 20.98]	0.49	8	14.03	[-1.87, 29.92]	8.40E-02	7	-9.86	[-27.85, 8.13]	0.28	40	-2.1	[-11.51, 7.31]	0.66										
Meta-analysis results																											
meta TOPMed + UK Biobank																											
Inverse-variance fixed effects										Random effects*																	
Gene	Group	ECG	Carrier	beta	95% CI	P value	beta	95% CI	P value	Carrier	beta	95% CI	P value	beta	95% CI	P value	beta	95% CI	P value								
<i>SCN5A</i>	LOF	RR	28	47.4	[-6.17, 100.93]	0.08	46.0	[-25.10, 119.07]	0.20	74	14.6	[-19.02, 48.16]	0.40	30.0	[-28.20, 80.14]	0.35											
		PR	27	22.1	[12.86, 31.28]	2.65E-06	22.1	[12.86, 31.28]	2.65E-06	70	38.1	[31.98, 44.26]	4.33E-34	30.3	[12.23, 48.44]	0.001											
	LOF	PWD	16	6.0	[-10.4, 13.01]	0.095	5.6	[-3.54, 14.75]	0.23	58	15.5	[-11.46, 19.50]	4.38E-14	10.9	[-0.29, 22.15]	0.06											
		QRS	17	8.0	[2.36, 13.68]	5.50E-03	8.0	[2.36, 13.68]	5.50E-03	60	14.2	[10.78, 17.64]	4.69E-16	12.0	[4.69, 19.20]	1.20E-03											
LOF	QTc	24	4.3	[-5.18, 13.71]	0.38	3.8	[-9.63, 17.17]	0.58	64	1.1	[-5.60, 7.74]	0.75	1.7	[-7.53, 10.88]	0.72												

Note: ECG, electrocardiogram; CI, confidence interval; LOF, high-confidence loss-of-function variants; meta, meta-analysis; PWD, P-wave duration; * if random effects meta-analysis using Paule-Mandel estimator failed the DerSimonian-Laird estimator for tau^2 was used instead

Supplemental Table XVII. Carriers of rare variants in long QT syndrome genes among individuals with prolonged QTc

Phenotype	Variant set	TOPMed 12-lead			UK Biobank 31-lead			UK Biobank 12-lead			Total		
		N	Carrier	Percentage	N	Carrier	Percentage	N	Carrier	Percentage	N	Carrier	Percentage
All participants	<i>KCNQ1 and KCNH2 loss-of-function, pathogenic and likely pathogenic variants</i>	26976	67	0.25	20366	35	0.17	7013	8	0.11	54355	110	0.20
	<i>Long QT syndrome gene panel protein-altering rare variants</i>	26976	1289	4.78	20366	834	4.10	7013	289	4.12	54355	2412	4.44
	<i>KCNQ1 and KCNH2 loss-of-function, pathogenic and likely pathogenic variants</i>	26976	8083	29.96	20366	4368	21.45	7013	1502	21.42	54355	13953	25.67
QTc prolongation (QTc interval \geq 460ms)	<i>KCNQ1 and KCNH2 protein-altering rare variants</i>	1789	14	0.78	487	9	1.85	309	0	0.00	2585	23	0.89
	<i>Long QT syndrome gene panel protein-altering rare variants</i>	1798	125	6.95	487	29	5.95	309	10	3.24	2594	164	6.32
	<i>KCNQ1 and KCNH2 loss-of-function, pathogenic and likely pathogenic variants</i>	1798	619	34.43	487	98	20.12	309	66	21.36	2594	783	30.19
QTc prolongation (QTc interval \geq 480ms)	<i>KCNQ1 and KCNH2 protein-altering rare variants</i>	448	10	2.23	138	5	3.62	93	0	0.00	679	15	2.21
	<i>Long QT syndrome gene panel protein-altering rare variants</i>	448	33	7.37	138	16	11.59	93	2	2.15	679	51	7.51
	<i>KCNQ1 and KCNH2 loss-of-function, pathogenic and likely pathogenic variants</i>	448	171	38.17	138	33	23.91	93	17	18.28	679	221	32.55
QTc prolongation (QTc interval \geq 500ms)	<i>Long QT syndrome gene panel protein-altering rare variants</i>	108	4	3.70	59	2	3.39	37	0	0.00	204	6	2.94
	<i>KCNQ1 and KCNH2 loss-of-function, pathogenic and likely pathogenic variants</i>	108	10	9.26	59	9	15.25	37	2	5.41	204	21	10.29
	<i>Long QT syndrome gene panel protein-altering rare variants</i>	108	42	38.89	59	14	23.73	37	8	21.62	204	64	31.37

Note: Rare variants were defined as having MAF<0.1%. Protein-altering was defined in all cohorts to include at least: inframe deletions/insertions, frameshift deletions/insertions, missense, stoploss, stopgain, startloss and splice variants.

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